NOV 16 1916
LIBRARY

VOLUME 18 NUMBER 5

THE ARCHIVES
OF
INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston — THEO. C. JANEWAY, Baltimore

GEORGE DOCK, St. Louis — WARFIELD T. LONGCOPE, New York

W. S. THAYER, Baltimore

NOVEMBER 15, 1916

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879

CONTENTS OF VOLUME XVIII

JULY, 1916. NUMBER 1

PAGE

Introduction to the Third Report of the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital. J. F. Siler, M.D., P. E. Garrison, M.D., and W. J. MacNeal, M.D., New York 1

The Hereditary Factor in Pellagra. C. B. Davenport, Ph.D., Cold Spring Harbor, Long Island, N. Y. 4

A Study of the Heredity of Pellagra in Spartanburg County, South Carolina. Elizabeth B. Muncey, M.D., Cold Spring Harbor, Long Island, N. Y. 32

Studies in Cerebral Fat Embolism. With Reference to the Pathology of Delirium and Coma. Harry Gauss, M.D., Chicago 76

A Critical Consideration of Systemic Blastomycosis. With Notes on Certain Special Features and Report of Five Cases. H. Windsor Wade, M.D., and George S. Bel, M.D., New Orleans 103

Metabolism Studies Before and After Splenectomy in a Case of Pernicious Anemia. O. H. Perry Pepper, M.D., and J. Harold Austin, M.D., Philadelphia 131

Book Review: Modern Medicine. Its Theory and Practice. In Original Contributions by American and Foreign Authors. Edited by Sir William Osler, Bart., M.D., F.R.S. 136

AUGUST, 1916. NUMBER 2

PAGE

Dietary Deficiency as the Etiological Factor in Pellagra. Edward B. Vedder, M.D., Washington, D. C. 137

The Incidence of Pellagra in Spartanburg County, S. C., and the Relation of the Initial Attack to Race, Sex and Age. J. F. Siler, M.D., P. E. Garrison, M.D., and W. J. MacNeal, M.D., New York .. 173

The Lime Deficiency of Diapetes. Max Kahn, M.D., Ph.D., and Morris H. Kahn, M.D. 212

Further Studies in the Inactivation of Pepsin. The Effect of Various Salts and Alkaline Substances. Walter W. Hamburger, M.D., and Benjamin Halpern, M.D., Chicago 228

The Rate of Absorption of Various Digitalis Preparations from the Gastro-Intestinal Tract. Charles C. Haskell, C. S. McCants and F. P. Gardner, Richmond, Va. 235

Ventricular Escape with Observations on Cases Showing a Ventricular Rate Greater Than That of the Auricles. Paul D. White, M.D., Boston 244

A Study of Proteins in Urine, and a Comparison of Gravimetric and Nephelometric Methods for Their Estimation. J. T. W. Marshall, H. W. Banks, 3d, and S. S. Graves 250

Transient Auricular Fibrillation. An Electrocardiographic Study. Edward B. Krumbhaar, M.D., Philadelphia 263

The Archives of Internal Medicine

Vol. XVIII NOVEMBER, 1916. No. 5

THE ACTION OF THE SO-CALLED FEMALE REMEDIES ON THE EXCISED UTERUS OF THE GUINEA-PIG *

J. D. PILCHER, M.D., G. E. BURMAN
AND
W. R. DELZELL
OMAHA

Introduction: The present paper is an introduction to a study of the so-called female remedies, drugs which have had more or less extensive clinical use, but which have not been subjects of thorough pharmacologic or clinical study. Judging from the large number of preparations of a proprietary or "patent" nature containing one or more of these drugs that are on the market at present, we must regard them as still extensively used. The purpose of the investigation was to determine whether any of the group possessed actions that could be referred to the uterus.

In this paper are presented their actions or lack of action on strips of the excised uterus of the guinea-pig. The method has certain limitations. A few experiments on strips of intestine indicate that the action is in no manner specific to the uterus. It seems safe to conclude, however, that if there is a positive action on the excised uterus, whether stimulation or depression, that a similar action would be exhibited on the uterus in situ if the drug reached the organ in a like concentration; such experiments on the uterus in situ are contemplated. In the text certain conclusions are drawn relative to the concentration of the drugs used in this work and the possibility of like concentrations being obtained in the body.

It may not be amiss to state at this place, that while a large number of the drugs studied exert definite actions on strips of the isolated

* Submitted for publication June 26, 1916.
* From the Pharmacologic Laboratories of the University of Nebraska, College of Medicine, Omaha, and Western Reserve University, Cleveland.
* This investigation was undertaken at the suggestion of the Therapeutic Research Committee of the American Medical Association and the Association assumed part of the expense of the investigation.

uterus, it is highly improbable that the concentrations necessary to elicit the action could be introduced into the body.

Methods: The usual methods were followed. A longitudinal strip of the uterus of the guinea-pig was attached to a muscle lever and immersed in a bath (50 c.c.) of Tyrode's fluid, kept well oxygenated by a constant stream of oxygen. The bath was kept at a fairly uniform temperature, about 38 C., although occasional variations did not seem to influence the action. The movements of the lever were recorded on a revolving drum. Usually there was a latent period of about twenty or thirty minutes before the regular contractions were initiated; sometimes the latent period was shorter and often much longer. Six experiments were usually carried on at the same time, strips from the same

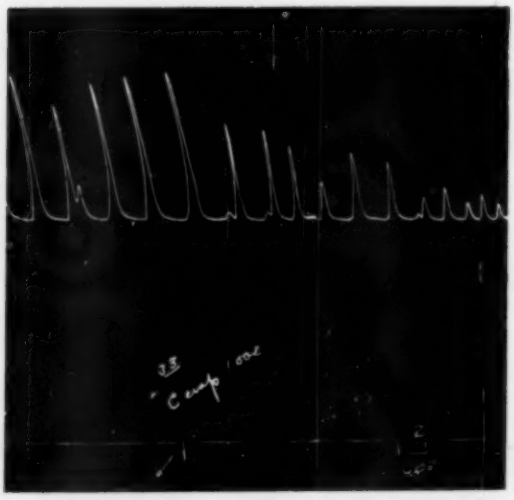

Fig. 1.—Aletris farinosa (unicorn root); Experiment 65b; the evaporated fluidextract to make a 1 to 1,000 solution was added at "1"; "2" is a time tracing of sixty seconds.

uterus being used. Frequently all strips from a given uterus failed to contract; again one strip failed to contract and others contracted well. In the later stages of pregnancy, when there is a larger amount of tissue, parts of the uterus were occasionally kept on ice over night and used on the next day, and rarely on the third day. As others have found, the pregnant uterus, especially in the later stages, usually contracts more vigorously than the virgin uterus and there are fewer inactive uteri in the pregnant group; for this reason the pregnant organ was usually employed. The action of a given drug sometimes presented differences between the virgin and the pregnant uterus; these differ-

ences will be discussed under the individual drugs. After obtaining a satisfactory control tracing of the normal contraction, the drug was added to the bath and the tracing continued for about fifteen minutes before transferring to fresh stock solution; occasionally the drug was allowed to act for a much longer period.

Preparations of the Drugs Used:[1] The fluidextract, the evaporated fluidextract and the infusion were employed. The fluidextract was used in the larger number of experiments, for the results with it did not differ materially from those with the evaporated extract. The fluidextracts used contained from 40 to 60 per cent. alcohol. Control experiments, with percentages of alcohol about the same as the fluidextracts made in the bath, were practically without action on the strips of the uterus; nevertheless, a large number of control experiments were made with the evaporated fluidextracts of most of the drugs and with but few exceptions, to be discussed under the individual drugs, the results did not differ materially from those of the fluidextract. Further, all but three of the fluidextracts (*Chamaelirium luteum, Leonurus cardiaca* and *Dioscorea villosa*) precipitated when added to the bath, and as many of the precipitates were very heavy, it was thought that a more intimate mixture would occur if the fluidextracts were added directly to the bath. When evaporated, the fluidextract was not exposed to a temperature higher than from 50 to 60 C.

Concentration of the Drugs Used: It was aimed to use a concentration of the drug that would approximate, therapeutically, the concentration in the blood under the most favorable conditions. If we assume that the average dose of the fluidextracts (2 c.c.) be absorbed promptly and equally distributed throughout the tissues of the body, the concentration in an adult (60 kg.) would be about 1 to 30,000; if all of the drug remained in the blood, a phenomenon, of course, that is inconceivable, the concentration would be about 1 to 2,000. The majority of the experiments were made with a much higher concentration than this (1 to 1,000); in other words, the concentrations used were greater than the highest conceivable concentration that could be

1. All the preparations used were furnished by the American Medical Association chemical laboratory. The crude drugs were identified and found true to name as follows: by Prof. Henry Kraemer: *Aletris farinosa, Caulophyllum thalictroides, Cypripedium pubescens, Dioscorea villosa, Ichthyomethia piscipula, Leonurus cardiaca, Mitchella repens, Passiflora incarnata, Pulsatilla pratensis, Scrophularia nodosa* (*marylandica*), *Scutellaria lateriflora, Senecio aureus, Valeriana officinalis, Chamaelirium luteum* and *Acer spicatum;* by Prof. E. N. Gathercoal: *Viburnum opulus, Viburnum prunifolium* and *Cnicus benedictus.* One each of the following fluidextracts was made by L. E. Warren of the American Medical Association chemical laboratory from the authentic drugs: *Acer spicatum, Viburnum prunifolium, Viburnum opulus* and the bark of the stem of the *Viburnum prunifolium;* all other fluidextracts were made by different firms and their identities were not established, but as the actions of two preparations of each drug were similar, their identity is probably authentic.

obtained therapeutically. As there were many exceptions to the average result, this strength was increased to 1 to 500 with some of the drugs without altering the type of action; occasionally more dilute solutions were effective. The strips were placed in fresh Tyrode solution before the addition of a different drug.

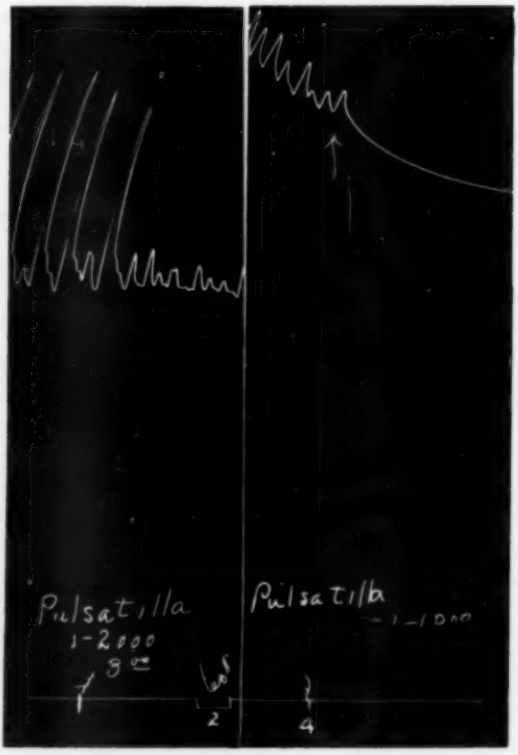

Fig. 2.—Pulsatilla pratensis (pulsatilla); Experiment 91c, late pregnancy; the fluidextract to make a 1 to 2,000 solution was added at "1"; contractions were not resumed and when placed in a fresh bath the strip went into a state of very great tone, and pulsatilla, 1 to 1,000 at "4" again caused cessation of the contractions. The tracing is interrupted between "2" and "4."

The Phenomena to Be Discussed: The action of the drugs was examined as affecting the rate and amplitude of excursion and the state of the muscular tone, these being considered the factors that determine the stimulant, depressant or negative action of the drugs. The rate may be considered an indication of the muscular irritability; the excursion, of the expulsive or parturient efficiency, and the tone as

an indication of the postpartum, styptic and, together with the excursion, of the abortifacient efficiency of a drug. The term "rate" always refers to the number of contractions per unit of time, and not to the duration of the individual contraction. The degree of relaxation of the strip was taken as the indication of the muscular tone. There is a close interrelation between rate, amplitude and tone. Under average conditions an increased rate usually prevents complete relaxation, so that apparently the muscular tone of the strip is increased. In such

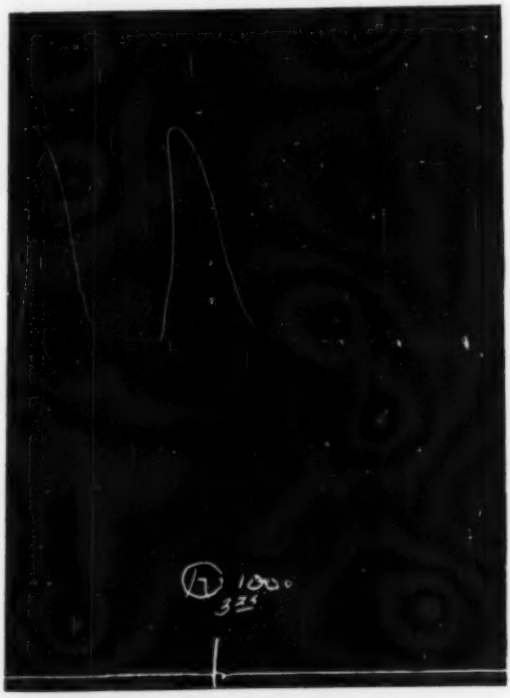

Fig. 3.—Ichthyomethia piscipula (Jamaica dogwood); Experiment 98d, late pregnancy; the fluidextract was added at "1" to make a 1 to 1,000 solution.

cases, however, there may be no actual increase of the tonicity of the muscular substance. Occasionally there was either an increase or decrease of tone with little or no change in rate or amplitude of the contractions. This would indicate a direct action on the muscular tone. In vigorously contracting uteri the rate is usually infrequent, so that there is plenty of time for complete relaxation. Under such conditions there may be considerable variation in the rate and amplitude without variation in the tone; this is especially true in advanced

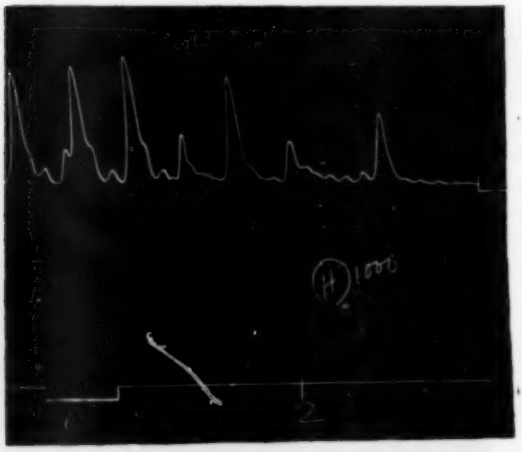

Fig. 4.—Scrophularia marylandica (figwort); Experiment 88b, late pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "2"; no contractions were made for ten minutes after the end of the tracing, when the experiment was terminated.

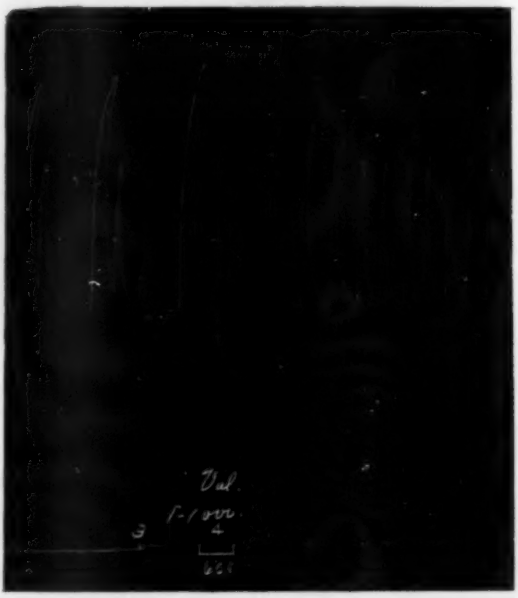

Fig. 5.—Valeriana officinalis (valerian); Experiment 51b, about midterm; the fluidextract to make 1 to 1,000 solution was added at "3"; "4" is a time tracing of sixty seconds.

stages of pregnancy. There are, however, instances of very great amplitude of excursion with rapid rate, so that here, too, an increase in tone may be more apparent than real. With this one exception, the impression that we have gained from this work is that the amplitude of the excursion is of greater import in judging the action of a drug than is the effect on the tone of the muscle. Indeed, it seems to us

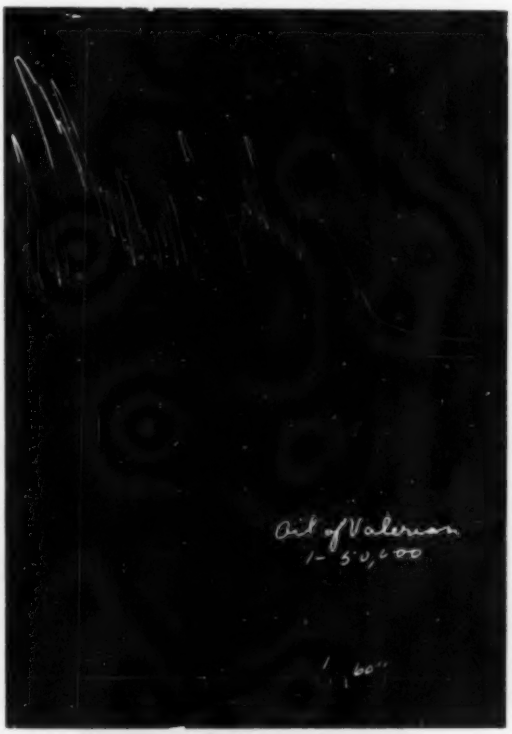

Fig. 6.—Oil of valerian; Experiment 109f, late pregnancy; oil of valerian to make a 1 to 50,000 solution introduced at "1"; the strip made a few small contractions later.

that there may be an actual muscular depression with apparent increase of the tone, for there are instances of an increased rate with a decreased amplitude of excursion in which the strip does not relax to the original state for lack of time only.

A good illustration in point is furnished by the work of Lieb[2] on viburnum. Lieb states that this drug increases the rate and tone, but diminishes the amplitude; the impression is that the drug really stimulates. Judging from his illustration, we conclude that there is no stimulation, for we think that fre-

2. Lieb: Am. Jour. Obst., 1914, lxix, 28.

quent small contractions are much less efficacious than fewer more vigorous ones, in expelling a fetus at any rate.

Of course, variation in amplitude (decrease or increase) may be balanced by variation in rate (increase or decrease), so that the end-result is practically the same. The points in question are well illustrated in the valerian series. This drug, with very few exceptions, considerably lessened the amplitude of the excursions, while the tone was unaffected in somewhat more than one half the experiments, and occasionally apparently increased. However, the tone

Fig. 7.—Cypripedium pubescens (lady's-slipper); Experiment 93d, late pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "1"; no contractions were made for six minutes after the end of the tracing; this is a greater depression than the average experiment shows; "2" is a time tracing of sixty seconds.

was decreased, as a rule, in those experiments in which there was a decreased rate, thus allowing time for more complete relaxation of the muscular strip. On the other hand, the tone was unaffected or occasionally even increased when the rate was somewhat increased (this usually secondary to a considerably lessened amplitude). When the rate was unchanged the tone was lessened. There were exceptions to these generalizations.

Natural Variations in Control Experiments: The action of the muscular strips varies greatly in uniformity. Frequently the rate and amplitude of contraction were quite uniform, but again very irregular. A uterus that had been contracting regularly for several minutes would miss a few contractions, or, vice versa, a strip that had been contracting poorly would begin regular vigorous contractions. This irregularity of action necessitated a large number of experiments to prevent such natural variations being taken for the action of the introduced drug,

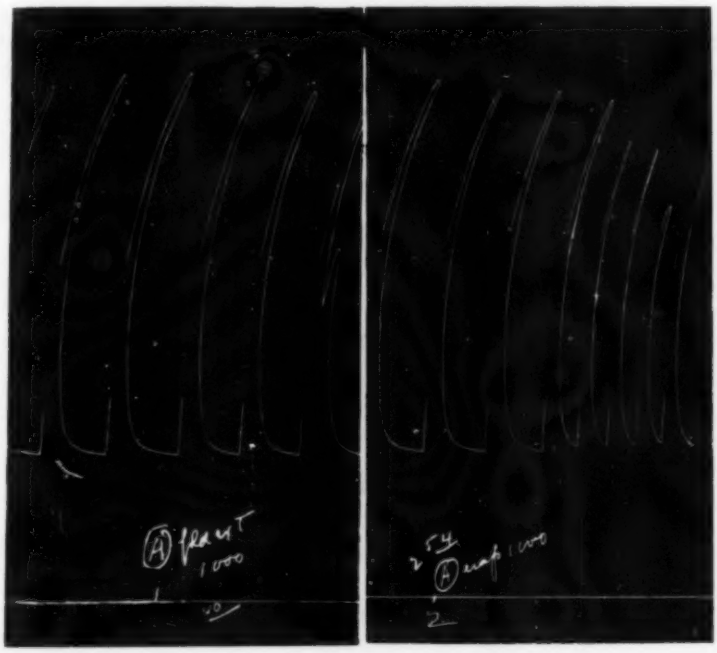

Fig. 8.—Dioscorea villosa (wild yam); Experiment 63b, advanced pregnancy; Dioscorea villosa (fluidextract) 1 to 1,000 added at "1"; at "2" the evaporated fluidextract to make 1 to 500; the tracing is interrupted for a few minutes between "1" and "2."

for not infrequently on the addition of one of the inert drugs the action changed materially, either a great increase or decrease in function, so without careful control experiments erroneous interpretations might have been made. When such results occurred with the same drug, it is significant that they were not always in the same direction, some tending toward depression and others toward stimulation of one or more functions. Frequently on transferring a strip to fresh stock

solution contractions ceased for a longer or shorter time or their character was changed completely. While the experiments with alcohol indicate that the alcoholic content of the fluidextracts played no definite part in the results, yet it may be that an occasional variable result may have been due to the alcohol. The text will show that this was but an occasional factor, if it played any part at all. Infrequently strips went into tonic contraction of indefinite duration when placed into a fresh bath. In this state they were very resistant to depressant drugs.

In view of the many natural variations, it seems best not to attempt too exact a classification, so that experimental results were considered to be negative unless they were fairly constant in nature. The experi-

Fig. 9.—Senecio aureus (life root); Experiment 26a, early pregnancy; Senecio aureus (fluidextract) to make a 1 to 1,000 solution added at "2," and, fifteen minutes later, to make a 1 to 500 solution, at "3"; the tracing was interrupted between "2" and "3."

ments are all listed in the accompanying table, as to rate, amplitude and tone, with the different preparations of the drug and the strength of the solution used.

The Results of the Experiments: These are arranged in the text according to the degree of activity of the drug, presenting, first, those drugs that depress, the single drug that stimulates, and finally the inactive preparations:

The Depressant Group: The following drugs are markedly depressant: *Aletris farinosa, Pulsatilla pratensis, Scrophularia nodosa* and *Ichthyomethia piscipula;* somewhat less active: *Valeriana officinalis* (the oil is very active) and *Cypripedium pubescens;* possessing but slight activity: *Dioscorea villosa, Scutellaria lateriflora* and *Senecio aureus.*

The single stimulant drug is *Caulophyllum thalictroides.*

The inactive drugs are as follows: *Chamelirium luteum, Leonurus cardiaca, Passiflora incarnata, Mitchella repens, Viburnum prunifolium* and *V. opulus, Acer spicatum, Cnicus benedictus, Carduus marianus* and *Castanea dentata.*

Aletris farinosa (unicorn root): Unicorn root is an active depressant (Fig. 1). The 1 to 1,000 solution of the fluidextract decreased

Fig. 10.—Scutellaria lateriflora (skullcap); Experiment 88a, late pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "1"; "2" is a time tracing of sixty seconds. The action is usually less marked than in this tracing.

the amplitude of excursion in each of thirteen experiments. The results were not quite so uniform with the evaporated extract, but when the solution was increased to 1 to 500 two of the negative experiments also showed depression. The decrease in the amplitude was considerable, being quite marked in about one-half the cases; several times the contractions were interrupted on the addition of the drug and were not resumed at all. The tone was practically not affected.

The rate was usually decreased with the alcoholic preparations, but often unaffected when the evaporated extract was used. The infusion was inactive.

Pulsatilla pratensis (pulsatilla): Pulsatilla is a very active depressant, although the strips from different pigs did not react quite uniformly. The action is the same as that of the other depressant drugs, differing only in degree. Even a 1 to 2,000 solution caused a marked depression in excursion in the two experiments in which it was used (Fig. 2). When effective, the decrease in the amplitude was usually

Fig. 11.—Caulophyllum thalictroides (blue cohosh); Experiment 84a; the infusion to make a 1 to 500 solution was added at "2" and the fluidextract to make a 1 to 1,000 solution (of the extract alone) was added at "3." The tracing shows the inactivity of the infusion and the great activity of the alcoholic preparation; the increase in tone was not due to the combined action of the infusion and the fluidextract, for the former was uniformly inactive and the latter always active.

quite prompt and considerable; once the activity ceased promptly on the addition of the 1 to 1,000 solution and was not renewed. The tone was not affected; the rate was slowed in about one-half the cases. The infusion was quite inactive in five experiments, four of them with the 1 to 500 solution and one with the 1 to 1,000.

The action was uniformly depressant on eight strips from two pigs, but with a third pig the contractions of three of six strips were not influenced by the 1 to 1,000 solution, while the others were depressed much less than the strips from the other pigs with the same strength of solution. Two of the

latter strips ceased to contract at once when the solution was increased to 1 to 500, but a third strip, aside from missing two or three contractions on the addition of the drug, contracted practically normally during about twenty minutes. The difference in the reaction in the three pigs is not explainable by the stage of pregnancy.

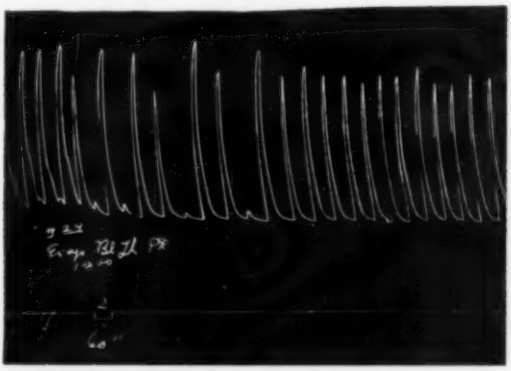

Fig. 12.—Cnicus benedictus (blessed thistle); Experiment 95c, about mid-term; the evaporated fluidextract to make a 1 to 200 solution was added at "1"; "2" is a time tracing of sixty seconds.

Fig. 13.—Viburnum opulus (cramp bark); Experiment 4, virgin cat; Viburnum opulus (fluidextract) to make a 1 to 500 solution added at "3," and to make a 1 to 250 solution at "4"; "2" is a time tracing of sixty seconds. (There seemed to be a progressive increase in tone and amplitude when the drug was added.)

Ichthyomethia piscipula (Jamaica dogwood): This preparation is an active depressant; on the addition of the 1 to 1,000 solution of the fluidextract after one or two less vigorous contractions, they cease entirely (Fig. 3). This was the result in five cases, four strips of which were allowed to remain in the solution for forty-five minutes

SUMMARY OF THE ACTION OF THE DRUGS ON THE RATE AND AMPLITUDE OF THE EXCURSIONS AND ON THE TONE OF THE STRIPS OF THE UTERUS *

Drug	Strength of Solution	Number of Experiments	Rate			Amplitude			Tone		
			Increase	Decrease	Negative	Increase	Decrease	Negative	Increase	Decrease	Negative
Aletris farinosa—											
Fluidextract	1 to 1,000	12	2	8	2	0	12	0	1	2	9
Fluidextract, evap.	1 to 1,000	12	1	2	9	1	8	3	0	0	12
Fluidextract, evap.	1 to 500	3	2	1	0	0	3	0	0	0	3
Infusion	1 to 1,000	2	1	0	1	0	1	1	0	0	2
Infusion	1 to 500	2	0	0	2	0	0	2	0	0	2
Pulsatilla—											
Fluidextract	1 to 2,000	2	1	1	0	0	2	0	0	0	2
Fluidextract	1 to 1,000	12	1	6	5	0	9	3	0	3	9
Fluidextract	1 to 500	2	0	1	1	0	1	1	0	1	1
Infusion	1 to 500	5	0	0	5	0	0	5	0	0	5
Ichthyomethia—											
Fluidextract	1 to 1,000	5	0	5	0	0	5	0	4	0	1
Infusion	1 to 500	2	1	1	0	0	1	1	0	0	2
Scrophularia—											
Fluidextract	1 to 1,000	8	0	4	4	0	8	0	0	2	6
Infusion	1 to 1,000	3	0	0	3	0	3	0	0	0	3
Infusion	1 to 500	3	1	1	1	0	3	0	0	0	3
Valerian—											
Fluidextract	1 to 2,000	5	0	2	3	0	2	3	0	2	3
Fluidextract	1 to 1,000	29	5	13	11	4	22	3	2	11	16
Fluidextract	1 to 500	14	3	9	2	0	14	0	1	12	1
Fluidextract, evap.	1 to 1,000	21	4	11	6	0	20	1	1	12	8
Fluidextract, evap.	1 to 500	6	1	1	4	0	6	0	1	1	4
Infusion	1 to 1,000	12	1	1	10	3	0	9	1	0	11
Infusion	1 to 500	8	2	1	5	1	1	6	1	0	7
Oil of valerian	1 to 100,000	1	0	1	0	0	1	0	0	1	0
Oil of valerian	1 to 50,000	4	1	3	0	0	4	0	0	3	1
Oil of valerian	1 to 10,000	10	0	10	0	0	10	0	0	10	0
Cypripedium—											
Fluidextract	1 to 1,000	8	1	5	2	0	8	0	0	0	8
Fluidextract	1 to 500	2	0	1	1	0	2	0	0	0	2
Infusion	1 to 500	3	1	0	2	0	3	0	0	0	3
Scutellaria—											
Fluidextract	1 to 1,000	9	0	5	4	1	6	2	0	0	9
Fluidextract	1 to 500	2	0	2	0	0	2	0	0	1	1
Fluidextract, evap.	1 to 1,000	4	1	1	2	0	1	3	0	0	4
Infusion	1 to 500	6	0	1	5	0	2	4	0	0	6

* The interpretation of the results will be found in the text.

SUMMARY OF THE ACTION OF THE DRUGS ON THE RATE AND AMPLITUDE OF THE EXCURSIONS AND ON THE TONE OF THE STRIPS OF THE UTERUS *—(*Continued*)

Drug	Strength of Solution	Number of Experiments	Rate			Amplitude			Tone		
			Increase	Decrease	Negative	Increase	Decrease	Negative	Increase	Decrease	Negative
Dioscorea—											
Fluidextract	1 to 1,000	14	6	1	7	0	8	6	3	0	11
Fluidextract, evap.	1 to 1,000	5	3	0	2	0	2	3	2	0	3
Fluidextract, evap.	1 to 500	3	1	0	2	0	2	1	0	0	3
Infusion	1 to 1,000	3	0	0	3	0	0	3	0	0	3
Infusion	1 to 500	2	1	0	1	0	1	1	1	0	1
Senecia aureus—											
Fluidextract	1 to 1,000	11	2	2	7	2	4	5	3	4	4
Fluidextract	1 to 500	8	1	4	3	1	7	0	1	6	1
Fluidextract, evap.	1 to 1,000	6	0	0	6	0	0	6	0	0	6
Fluidextract, evap.	1 to 500	3	0	1	2	0	2	1	0	0	3
Infusion	1 to 1,000	5	0	0	5	1	1	3	1	0	4
Infusion	1 to 500	6	2	0	6	1	2	5	2	0	6
Caulophyllum—											
Fluidextract	1 to 2,000	3	0	3	0	0	3	0	3	0	0
Fluidextract	1 to 1,000	11	0	5	6	0	8	3	11	0	0
Fluidextract, evap.	1 to 1,000	8	0	8	0	0	8	0	8	0	0
Infusion	1 to 1,000	4	0	0	4	0	0	4	0	0	4
Infusion	1 to 500	4	0	0	4	0	0	4	0	0	4
Viburnum prunifolium—											
Fluidextract (virgin)	1 to 1,000	5	0	1	4	1	1	3	2	1	2
Fluidextract (pregnant)	1 to 1,000	8	1	1	6	2	1	5	4	1	3
Fluidextract (virgin)	1 to 500	5	2	1	2	0	2	3	3	1	1
Fluidextract (pregnant)	1 to 500	7	1	2	4	1	2	4	2	1	4
Fluidextract, evap.	1 to 1,000	4	0	0	4	1	1	2	0	0	4
Fluidextract, evap.	1 to 500	1	0	0	1	1	0	0	0	1	0
Infusion	1 to 1,000	4	0	0	4	2	0	2	0	0	4
Infusion	1 to 500	6	0	0	6	2	0	4	1	0	5
Fluidextract (bark of tree)	1 to 500	4	0	0	4	0	0	4	0	0	4
Infusion (bark of tree)	1 to 500	5	0	0	5	0	2	3	0	0	5
Viburnum opulus—											
Fluidextract (virgin)	1 to 1,000	5	0	1	4	0	1	4	3	1	1
Fluidextract (pregnant)	1 to 1,000	8	2	1	5	2	4	2	0	0	8
Fluidextract (virgin)	1 to 500	7	1	0	6	2	1	4	4	0	3
Fluidextract (pregnant)	1 to 500	10	3	2	5	0	6	4	0	0	10
Fluidextract, evap.	1 to 1,000	6	0	1	5	0	1	5	0	0	6
Fluidextract, evap.	1 to 500	2	0	0	2	0	0	2	0	0	2
Fluidextract, evap.	1 to 100	1	1	0	0	0	1	0	1	0	0
Infusion	1 to 1,000	1	0	0	1	0	0	1	0	0	1
Infusion	1 to 500	4	1	2	1	1	2	1	0	1	2
Infusion	1 to 100	1	0	0	1	0	0	1	0	0	1

SUMMARY OF THE ACTION OF THE DRUGS ON THE RATE AND AMPLITUDE OF THE EXCURSIONS AND ON THE TONE OF THE STRIPS OF THE UTERUS *—(*Continued*)

Drug	Strength of Solution	Number of Experiments	Rate			Amplitude			Tone		
			Increase	Decrease	Negative	Increase	Decrease	Negative	Increase	Decrease	Negative
Acer spicatum—											
Fluidextract	1 to 1,000	7	2	0	5	2	0	5	1	2	4
Fluidextract, evap.	1 to 1,000	5	1	1	3	2	0	3	1	1	3
Fluidextract, evap.	1 to 500	2	1	0	1	0	0	2	0	0	2
Cnicus benedictus—											
Fluidextract	1 to 1,000	8	0	1	8	1	1	7	0	1	8
Fluidextract	1 to 500	5	0	2	3	0	2	3	0	2	3
Fluidextract, evap.	1 to 1,000	12	4	1	7	8	0	4	8	0	4
Fluidextract, evap.	1 to 500	6	1	1	4	1	1	4	1	1	4
Fluidextract, evap.	1 to 200	10	0	7	3	0	3	7	0	0	10
Infusion	1 to 1,000	11	2	1	8	3	2	6	3	0	8
Infusion	1 to 500	6	2	0	4	1	1	4	2	0	4
Chamaelirium—											
Fluidextract	1 to 1,000	12	0	3	9	0	4	8	2	2	8
Fluidextract	1 to 500	4	0	1	3	2	1	1	2	1	1
Fluidextract, evap.	1 to 1,000	9	1	2	6	1	3	5	1	0	8
Infusion	1 to 1,000	5	0	0	5	0	1	4	1	0	4
Infusion	1 to 500	7	1	0	6	1	1	5	2	0	5
Leonurus—											
Fluidextract	1 to 1,000	8	2	1	5	0	3	5	0	0	8
Fluidextract, evap.	1 to 1,000	7	1	0	6	1	1	5	0	0	7
Infusion	1 to 500	7	4	0	3	0	4	3	1	0	6
Passiflora—											
Fluidextract	1 to 1,000	10	1	0	9	0	1	9	0	1	9
Fluidextract, evap.	1 to 1,000	5	0	2	3	2	1	2	2	0	3
Infusion	1 to 500	2	0	0	3	1	0	2	2	0	3
Mitchella—											
Fluidextract	1 to 1,000	7	2	0	5	2	3	2	2	0	5
Fluidextract, evap.	1 to 1,000	7	0	0	7	0	0	7	0	0	7
Infusion	1 to 500	3	0	0	3	0	1	2	0	0	3
Castanea—											
Fluidextract	1 to 1,000	9	0	1	8	1	2	6	0	0	9
Infusion	1 to 500	4	0	0	4	0	1	3	0	0	4

and made but one small contraction during that time, showing that the action is persistent. The tone was practically unaffected. The infusion is not so active, for while it depressed one strip considerably, a second was not influenced at all.

Scrophulario marylandica (figwort): Figwort actively lessened the amplitude of the excursions, secondarily decreased the rate and left the tone unaffected (Fig. 4). In each of eight experiments there was a marked decrease in excursion within from ten to fifteen minutes of the addition of the drug (1 to 1,000 of the fluidextract). Occasionally the effect was quite prompt, the contractions ceasing temporarily and then recurring some minutes later with considerably lessened amplitude. The rate was but secondarily affected, more often remaining the

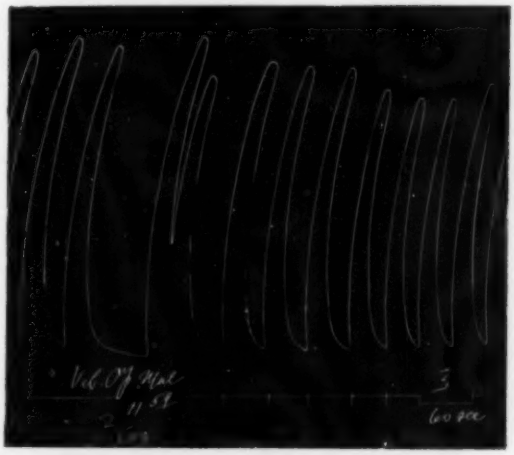

Fig. 14.—Viburnum opulus (cramp bark); pregnant guinea-pig; fluidextract Viburnum opulus to make a 1 to 500 solution added at "2."

same, but being frequently decreased somewhat. The tone was not altered. The infusion was also effective, as three cases exhibited a somewhat lessened excursion from the 1 to 1,000 solution. This action was augmnented by increasing the strength to 1 to 500. When the fluidextract was added to the bath already containing the infusion, the effect was additive.

Valerian: This drug very generally depresses, especially the amplitude of the excursion, somewhat less the tone and the rate. The rate may be increased, presumably secondary to the decreased excursion. The active principle is found in the fluidextract, the evaporated fluidextract, and in the oil of valerian, but not in the infusion; it is non-

volatile at 100 C., for the distillate from the fluidextract is inactive, while the residue retains virtually the original activity. It is probably a resin. Sodium valerate is practically inactive (Figs. 5 and 6).

The Fluidextract: In some fifty experiments with the 1 to 1,000 solution of the fluidextract and the evaporated fluidextract there was uniformly a depression of the muscle strips. The most striking effect was on the amplitude of the excursions, for this was decreased almost without exception, and in practically half the experiments the decrease was rather marked. The non-

Fig. 15.—Acer spicatum (maple bark); Experiment 51b, about midterm; infusion Acer spicatum to make a 1 to 250 solution added at "8."

evaporated fluidextract was somewhat more active than the evaporated extract. The rate was also diminished, although in about half the cases only; the action was not so great as on the amplitude. In about one fourth of the cases the rate was moderately increased; however, this did not indicate increase in function, but probably was secondary to the lessened amplitude, as was discussed in the introduction. The muscular tone was also decreased in about one half the experiments, as indicated by the tracings, but, actually, probably much more frequently than this, for the frequently increased rate masked the lessened tone by preventing complete relaxation. Recovery was usually rather

slow and imperfect. With but few exceptions the strips were contracting vigorously. The depressant action was also observed in two of five experiments with the 1 to 2,000 solution of the fluidextract.

As the strength of the solution was increased to 1 to 500 the depressant action became more marked. Of fourteen experiments with the fluidextract, without exception the amplitude was decreased and with but two exceptions the tone also was diminished. The amplitude was lessened in each of six cases with the evaporated extract, although the tone and rate were usually unaffected.

The Infusion: This preparation was inactive in a large series of cases (twelve with the 1 to 1,000 and seven of eight cases with the 1 to 500 solution). The inactivity was not due to the loss of a volatile substance during the

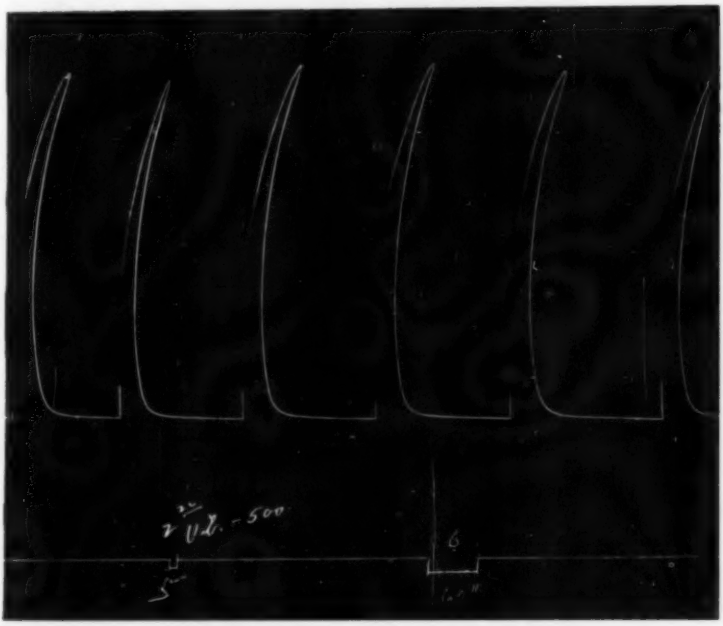

Fig. 16.—Viburnum prunifolium (black haw); Experiment 43b, late pregnancy; the fluidextract to make a 1 to 500 solution was added at "5"; fifteen minutes elapsed between the introduction of the drug and the end of the tracing.

making of the infusion, for infusions made in stoppered bottles at 45 C. were inactive. The distillate from the fluidextract was also practically inactive in eleven experiments, while the residue from the distillate, made up to the original volume, preserved practically the original activity of the fluidextract, proving that the active principle of valerian is nonvolatile (at 100 C.), and is not injured by boiling for a short time.

Sodium Valerate: Lieb[2] states that sodium valerate is inactive except in high concentrations, which are toxic; the actual concentration is not stated. In our work the 1 to 1,000 solution was practically inactive, while the same strength of the fluidextract was always depressant. Three of five experiments with the 1 to 1,000 solution gave negative results and two a slight decrease in

excursion, but one of the latter contracted vigorously after one hour in the valerate. Experiments with less concentrated solutions were negative. Similar strengths were without action on strips that were in a state of high tone.

Oil of Valerian: The oil very actively depresses the strips of the uterus, so that even the 1 to 100,000 solution lowers the amplitude and recovery from the action is very slight when the strips are placed in fresh stock solution. Only one experiment was made with the 1 to 100,000 solution, but as this action was similar to the somewhat stronger solutions, this was thought to be sufficient. The dilution of 1 to 50,000 caused a very marked depression in each of four experiments under different degrees of contractions (Fig. 6). The contractions of two strips were stopped at once, one of which had been contracting moderately and the other but slightly. The vigorous contractions of one strip were inhibited during about twelve minutes. The last strip was in a state of high and increasing tone without contracting and the tone was promptly lowered by the oil. More concentrated solutions allayed contractions at once and recovery was very poor and usually absent if the strip remained in the solution of the oil for even a very few minutes; ten minutes in the 1 to 10,000 solution was usually sufficient to prevent recovery in fresh stock solution. The tone was lowered in all experiments.

Fig. 17.—Castanea dentata (chestnut bark); Experiment 100a, early pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "3."

Cypripedium pubescens (lady's-slipper): Lady's-slipper lessened the amplitude of the excursions moderately but fairly constantly; secondarily, it slowed the rate in part of the experiments and left the tone unaltered. This result was obtained from twelve experiments with the 1 to 1,000 solution of the fluidextract. Two cases showed considerable depression of the amplitude (Fig. 7). The results were the same with vigorously and poorly contracting strips. The infusion in the strength of 1 to 500 also lowered the excursion somewhat.

Dioscorea villosa (wild yam): in about one-half the experiments this drug caused a lowering of the amplitude, in some of them considerably, in others slightly. An increased rate usually accompanied a decreased amplitude, otherwise the rate was not affected (Fig. 8). There was an occasional increase in tone. The results were similar with the fluid and the evaporated extract. The infusion is probably inactive.

The amplitude was lessened in eleven of twenty-two experiments with the 1 to 1,000 solution. In some of them the action was so slight as to be doubtful whether it was not simply a natural variation, rather than an action of the drug. In three of the experiments with lessened amplitude the tone was considerably increased, so that probably the change in excursion was secondary to this; all other experiments were without action on the tone, so that the occasional increase in tone is without significance. Four cases with the 1 to 500 solution gave irregular results. Three experiments with the 1 to 1,000 solution of the infusion were negative; one with the 1 to 500 solution gave an increased tone, but the other was negative. Most of the strips were contracting vigorously, but the initial activity of the strip did not influence the end-result.

Senecio aureus (liferoot): Again the majority of the cases showed this drug to have no constant action on the excised uterus. There was an indication that in high concentrations the drug was depressant.

Fig. 18.—Passiflora incarnata (passion flower); Experiment 69f, late pregnancy; the fluidextract to make 1 to 1,000 solution was added at "1"; "2" is a time tracing of sixty seconds.

With the fluidextract (1 to 1,000) both amplitude and tone were decreased in four of eleven experiments and as the solution was increased to 1 to 500, these functions were decreased in all but one of eight cases (Fig. 9). The depression from the higher concentration was quite marked, although recovery was fairly complete when the strip was placed in fresh stock solution. In the 1 to 1,000 solution neither the infusion nor the evaporated extract exhibited any action on the strips; in the stronger solution (1 to 500) the amplitude was lessened in about one fourth of the experiments with each preparation. Even the 1 to 250 solution was without action on one strip from

the virgin cat uterus during ten minutes and caused but slight decrease in rate and amplitude in a second. A 1 to 1,000 solution of the fluidextract of the drug made less than a 1 to 2,000 solution of alcohol.

Scutellaria lateriflora (skullcap): This drug exhibited a rather weak and inconstant depressant action (Fig. 10). The excursions were lessened somewhat in about two thirds of the experiments, the rate moderately slowed in one half of them; the tone was not affected. The slight action of the drug is illustrated by the fact that two strips contracted moderately after forty-five minutes in the 1 to 500 solution. Two of six experiments with the infusion 1 to 500 exhibited a slight depression of the amplitude.

Caulophyllum thalictroides (blue cohosh): Blue cohosh invariably caused a pronounced increase of tone or tetanus in all strips that gave any sign of activity and frequently initiated contractions in nonactive strips (Fig. 11). Rather promptly on the addition of the blue cohosh (fluidextract) the contractions either ceased entirely or became greatly lessened in amplitude, as the recording lever rose either considerably

Fig. 19.—Mitchella repens (squaw vine); Experiment 70c, about midterm; the fluidextract in a 1 to 1,000 solution.

above, to, or just a little below the maximal point previously attained, but always considerably above the midline between the highest and the lowest levels. Occasionally, when the strip was contracting but slightly or irregularly, the contractions persisted more or less, although the tone was increased. The usual picture, however, was a prompt increase in tone with practically cessation of the contractions, whether the strip had been contracting vigorously or just moderately. The decrease in amplitude, then, seemed to be purely secondary to the marked increase in tone. This tonic state was very persistent, over an hour in a few strips, but the other experiments were usually interrupted after from twenty to forty minutes, so that the strips could be used for other drugs. However, the usual experience was that the strips seldom recovered their normal condition after remaining in the blue cohosh solution for a few minutes. The typical action was caused by the 1 to 2,000 solution in a few experiments.

Further to test the activity of the drug it was added (1 to 1,000) to twelve strips that either had shown no signs of activity after being

in the bath for from twenty to sixty minutes or had ceased to contract after a period of activity; eight of these strips gave the usual increase in tone and four of these also started to contract. The 1 to 1,000 solution also increased the tone of one of three strips that had been rendered inactive by valerian; the cohosh was added directly to the valerian solution.

The infusion was practically inactive in strengths up to 1 to 500. Four experiments were made with the 1 to 1,000 solution, which was increased to 1 to 500. In all cases control experiments, made by adding the alcoholic solution directly to the infusion, gave the characteristic increase in tone. The active principle of the blue cohosh is not extracted in the aqueous preparations.

The experiments were made with uteri in all stages of pregnancy and with the virgin uterus as well. The action was similar in all of the conditions.

Cnicus benedictus (blessed thistle): This drug has practically no action on the excised uterus; even very high concentrations (1 to 200) have little action, but tend toward depression (Fig. 12). The fluidextract and the infusion were inactive. There was evidence of slight stimulation (increased amplitude and tone) in many of the experiments with the evaporated fluidextract, but this was not sufficiently great to be of significance. All stages of pregnancy were present.

The Fluidextract: The 1 to 1,000 solution was practically inactive, for eight of nine experiments were quite negative and the exception showed but slight depression. The extracts are made with 40 per cent. alcohol, which would make less than a 1 to 2,000 solution in the bath, so that the alcohol could have exerted little if any action. Strengthening the solution to 1 to 500 resulted in moderate depression in two of five experiments. In two experiments on strips from the virgin cat the 1 to 1,000 and the 1 to 500 solutions were without action. Even the 1 to 250 solution was inactive during ten minutes in one case and but slightly lessened the tone in the other. In the latter, however, the contractions were practically unchanged during fifteen minutes, so that the decrease in tone may have been no more than a natural variation.

The Infusion: The results were negative in the majority of cases, both with the 1 to 1,000 and the 1 to 500 solutions. The exceptional results were about equally divided between slight stimulation and depression, that is, probably merely just the natural variations met in control experiments.

The Evaporated Extract: In the 1 to 1,000 solution this increased the amplitude and the tone slightly in two thirds of the experiments (eight of twelve) and increased the rate in one third of them. Part of the increase in function was probably but the normal natural variations, for in some of the experiments there is a probability that the drug was introduced before the curve had become constant. This may explain the difference between the results with the fluid and the evaporated extract. At any rate it is significant that there was no evidence of depression. In view of the uniform inactivity of the fluidextract (in about the same number of experiments) this slight variation can be of no significance. Increasing the strength of the solution to 1 to 500 decreased the number of experiments that showed stimulation to one of six, while four gave negative results and the final one gave depression. With even stronger solutions (1 to 200) there was little permanent action

on the strips, although there was depression of the amplitude in part of them. Two of ten cases were quite negative. In the others one phenomenon was quite constant. On the addition of the drug there was a temporary cessation of the contraction over a period of time corresponding to two or three contractions. Following this brief period one half of the strips returned to the normal condition and remained so during thirty minutes or more, while the others were permanently depressed, considerably in two cases and but slightly in two others. The brief period of cessation of activity could bear little significance in the intact animal unless possibly by an intravenous injection of an enormous dose. The tone was unaffected. The results were similar in vigorously and poorly contracting strips. Citation of a single experiment will illustrate the inactivity of the drug.

Experiment 99: The strip was contracting vigorously. Blessed thistle solution (1 to 200) caused a brief cessation of contraction and then for a short time the contractions were more vigorous than the normal. After ninety minutes the strip was still contracting well although the amplitude was considerably lessened. Two hours later (three and one half hours after the addition of the drug) the strip was still quite active.

Carduus marianus: Several experiments with the 1 to 500 alcoholic solution of the seed of this drug showed it to be without activity.

Viburnum opulus (cramp bark): This drug was probably without action on the excised uterus of the guinea-pig. There was, however, a tendency toward increase in tone in the virgin pig (Fig. 13) and a slight decrease in excursion in the pregnant pig (Fig. 14). In either case the action was neither sufficiently great nor uniform to merit serious consideration, except possibly as it indicated lack of depression on the virgin uterus.

The Virgin Pig: The fluidextract was used. The increase in tone was fairly constant with the 1 to 1,000 solution (four or five cases) and persisted, though with a decreasing percentage, as the solution was increased to 1 to 500. Occasionally the increase was considerable. There was an infrequent and slight increase or decrease in rate and amplitude. In one of two cases with a 1 to 250 solution there was still an increase in tone (rate and amplitude unchanged). In the second the tone was decreased slightly, possibly because there was less time for relaxation as the rate was somewhat increased. Even stronger solutions may show little evidence of depression. A 1 to 100 solution decreased the tone that had been raised by a 1 to 250 solution, but not below the normal. In a second case the tone was considerably increased by a 1 to 100 solution. Too much emphasis should not be placed on the apparent increase in tone from even strong solutions of *Viburnum opulus*, because the limited number of experiments may not exclude the natural variations in action. However, it is significant that there was no depression.

The Pregnant Pig: Two thirds of the cases exhibited a somewhat decreased amplitude with the fluidextract (1 to 1,000 and 1 to 500). The tone was not changed and the rate also was practically uninfluenced. The evaporated extract was without action except in a single case that gave a considerable increase in tone. The infusion was either quite negative or irregular in action, for a few cases showed either slight stimulation of depression. Even a 1 to 100 solution was without action. Practically all the strips from the pregnant uterus were contracting vigorously.

Acer spicatum (maple bark): This drug is said to be substituted for *Viburnum opulus*. It is probably quite void of activity, for in the majority of the experiments with the fluidextract the contractions were

not altered, although in a few experiments the excursions were slightly increased. When the strips were contracting regularly the infusion, even in strong solutions (1 to 250), did not change the curve (Fig. 15).

Viburnum prunifolium (black haw): With the possible exception of an insignificant increase in tone, *Viburnum prunifolium* was without action in this work (Fig. 16). This conclusion was drawn from a total of forty experiments. The slight increase in tone occurred with the fluidextract only, in about one half of twenty experiments. The action was similar in the virgin and the pregnant uteri. The details are found in the table. The increased tone was not secondary to an imperfect relaxation from an increased rate, for the rate was increased in but two of the experiments showing an increased tone. At best, the change in tone was always slight and probably of little significance. There was no evidence of depression in solutions up to 1 to 250 in a single experiment with the virgin cat. The infusion and the evaporated extract were without action in fifteen cases, although one of them gave a slight depression of tone. In the great majority of all experiments the rate and amplitude were unaffected and the variant cases were about equally divided between stimulation and depression.

The bark of the stem was inactive in the 1 to 500 solution of the fluidextract and of the infusion. In two experiments the 1 to 500 solution of both preparations (making a 1 to 250 in all) was inactive. In one experiment the strip was not contracting, but was increasing in tone. The tone remained above normal during fifty minutes' immersion in the viburnum, when oil of valerian (1 to 25,000) promptly lowered the tone below the normal.

Chamaelirium luteum (false unicorn): The results of a large number of experiments with this drug, in 1 to 1,000 and 1 to 500 solutions, demonstrate that it has no constant action. In the far greater number of experiments there was no demonstrable change in the movements of the strip. In the exceptional instances there was no uniformity in the action or in the function affected, indicating that they were in all probability merely natural variations. The variations may be of sufficient merit to discuss, however, for several times there was a marked increase in tone in two virgin and two pregnant uteri, the latter contracting vigorously. The action was especially noticeable in one virgin strip that had been contracting very slightly. Occasionally similar phenomena are met in control experiments, but as it occurred more frequently (four times) with this drug, it may have a little significance. Several times the strips were somewhat depressed, but increasing the solution to 1 to 500 did not further depress, so that such action was probably accidental. These experiments were met a little oftener with the evaporated alcoholic solutions, so that the alcohol was

not the cause of the depression. The infusion (1 to 1,000 and 1 to 500) was inactive.

Leonurus cardiaca (motherwort): The alcoholic solution of the drug were practically inactive, as but three of fifteen experiments gave a moderate decrease in excursion. The infusion (1 to 500) depressed the excursion, as a rule; although this was not marked and in some instances was rather doubtful, nevertheless, there was no sign of a stimulant action. It may be that a principle of slight activity is extracted in the aqueous but not in the alcoholic menstruum.

Castanea dentata (chestnut): The preparation is practically void of action, although occasionally there seemed to be evidence of slight depression. This was not of sufficient intensity to be of any significance (Fig. 17). The infusion was also without action. Nearly all the strips were very active. This preparation was used as an example of an indifferent bark to see whether the tannin or other constituents in any way influenced the activity of the muscular strips.

Passiflora incarnata (passion flower): This is an inactive drug (Fig. 18); nine of ten experiments with the fluidextract were practically negative and the exception gave an immaterial increase in tone and a decrease in amplitude. The evaporated extract gave irregular results and the infusion was negative. All the strips were contracting vigorously.

Mitchella repens (squaw vine): This also is practically inactive (Fig. 19). All experiments with the evaporated extract and the infusion were negative. With the fluidextract the results were somewhat irregular, as in about an equal number of cases there was either no action or an immaterial increase or decrease in excursion. The variations at best were slight and within the limits of the natural variations. The strips usually contracted vigorously, but the less active ones gave the usual results.

CONCLUSIONS

The drugs employed with but one exception manifest their actions on the amplitude of the contractions rather than on the tone or the rate of contraction. The action is essentially the same on the pregnant and on the virgin uterus.

The following drugs lower the amplitude of the excursion, as their primary action: *Aletris farinosa, pulsatilla pratensis, Scrophularia nodosa* and *Ichthyomethia piscipula* are very active in the strengths used; *Valeriana officinalis* (the oil is very active) and *Cypripedium pubescens* somewhat less active; *Dioscorea villosa, Scutellaria lateriflora* and *Senecio aureus* least of all.

Caulophyllum thalictroides puts the strips into tonic contraction or tetanus.

Chamaelirium luteum, Leonurus cardiaca, Passiflora incarnata, Mitchella repens, Viburnum opulus and *V. prunifolium, Acer spicatum, Cnicus benedictus, Carduus marianus* and *Castanea dentata* are inactive.

The following infusions only are active and they are less active than the corresponding alcoholic preparations: Leonurus, Scrophularia, Ichthyomethia and Cypripedium.

We are glad to express our indebtedness to Prof. Sollmann for reviewing the manuscript.

GLUCOSE FORMATION FROM PROTEIN IN DIABETES *

N. W. JANNEY, M.D.
NEW YORK

1. INTRODUCTION

The origin of carbohydrates from protein in the animal body has becomes a very firmly established fact in spite of the animated controversies of the past. Proteins have been demonstrated in numerous researches to yield carbohydrates in metabolism. The same holds true for many of the amino-acids, which enter into the constitution of proteins.[1] Indeed there is good existing evidence showing that this is to be regarded as a normal metabolic process.[2]

It is however in the study of diabetes that a knowledge of sugar formation from protein becomes very essential, for not only is protein food ingested by diabetics converted into glucose, but extensive formation of this monosaccharid is known to take place from the diabetic's own tissue proteins. The importance of these considerations has stimulated numerous experimental investigations. Although much new data have been obtained as a result, considerable obscurity still remains. This applies especially to the question of the exact extent of the conversion of protein into glucose, a weighty subject for a clear conception both of the diabetic process and of diabetic dietetics. In this laboratory during recent years considerable time has therefore been devoted to its study. It is the purpose of the present communication to call attention to the results of medical importance obtained in this work as well as to report further experimental data bearing on the subject of the dietary of diabetes.

2. CRITIQUE OF FORMER INVESTIGATIONS

Previous efforts to ascertain the amount of glucose arising from the breakdown of proteins in metabolism have met with so many experimental difficulties that in almost all cases the results obtained are

* Submitted for publication May 24, 1916.

* From the Chemical Laboratory of the Montefiore Home and Hospital for Chronic Invalids, New York City.

* Preliminary reports of the experiments detailed in this section were presented in papers read before the Society for Experimental Biology and Medicine, Jan. 19, 1916, and the College of Physicians, Philadelphia, June 7, 1916.

1. Lusk, G.: Phlorhizinglukosurie, Ergebn. d. Physiol., 1912, xii, 315. Dakin, H. D.: Jour. Biol Chem., 1913, xiv, 321.

2. Pflüger, E., and Junkersdorf, P.: Arch. f. d. ges. Physiol., 1910, cxxxi, 201. Williams, H. B., Riche, J. A., and Lusk, G.: Jour. Biol. Chem., 1912, xii, 369.

open to serious criticism. It seems therefore expedient rather to emphasize the various sources of error in this work than to indulge in an elaborate critical review, which has indeed been already done by others[3] who also quote the literature extensively. The human diabetic has been in the past the subject most frequently selected for experiments of this nature.[4] Various proteins were fed to glycosuric patients and the influence on the sugar excretion observed. The results showed a rise in the glycosuria following the ingestion of protein, but very little certainty as to the extent of either absolute or relative sugar production from protein can be attached to this work for reasons to be stated.

In order to ascertain by means of feeding experiments the extent of glucose formation from ingested proteins it is necessary to demonstrate that all the fed material is digested and absorbed and that all the glucose arising from this material and no more, originates from this protein. These conditions can hardly be afforded by the human subject, as will now be brought out. In most cases of diabetes mellitus a certain amount of oxidation of glucose takes place. Moreover the capacity of the human diabetic to utilize glucose frequently may undergo considerable daily variation, even when the diet remains the same. It is also possible that glucose originating from food protein may be in part synthetically used in the formation of various body substances or be deposited as glycogen. In regard to these last considerations there are very few definite data as yet on record for the human diabetic.

The reliability of such metabolic experiments is dependent on the complete assimilation of the protein fed. In the former experiments referred to this important matter has not been adequately controlled. The important physiologic factors in this regard will be discussed later in this communication. It may suffice to mention here that the completeness and rapidity of absorption of protein is dependent not only on the amount and physical condition of such food, but also on the nature of other constituents of the diet. Experiments on human diabetic individuals, in which a given amount of protein is superimposed on other diet, are therefore rather uncertain.

It would thus seem advisable to use fasting diabetics for such experiments. The effect of starvation on the human subject is, however, as is so well demonstrated by Allen's researches, immediately to

3. For literature concerning the formation of sugar from protein see the following: Cremer, M.: Ergebn. d. Physiol., 1903, i, 803. Pflüger, A.: Arch. d. ges. Physiol., 1903, xcix, 1; Ibid., 1904, ciii, 1. Langstein, L.: Ergebn. d. Physiol., 1902, i, 63; Ibid., 1904, iii, 453. Falta, W.: Ztschr. f. d. inn. Med. u. Kinderh., 1908, ii, 99.

4. See the work of Lüthje, von Noorden, Mohr, Therman, and Falta.

increase the ability of the organism to oxidize glucose. We cannot then expect glucose arising from ingested substances to be excreted quantitatively by otherwise fasting diabetics. This is undoubtedly a source of error in certain human experiments already reported, in which protein has been administered to patients after days of greatly restricted diet. Another and contrary effect of feeding quantities of sugar-forming proteins to diabetics is to lower the tolerance of the organism for glucose, with consequent uncertainty in the results. This is very evident in certain of Mohr's experiments. Still another disturbing factor in the use of the human diabetic is the fact that muscular exercise may decrease the glycosuria under some circumstances, but increase it under others.[5] But the great difficulty of preventing diabetics breaking diet is very probably the chief cause of error in such human experiments.

Through one or more of these sources of error the results of protein feeding experiments and clinical observations are rendered dubious. Conclusions drawn from these results cannot therefore be regarded as established. Among such may be mentioned those of Lüthje, von Noorden, and Falta, who hold that relative differences in the influence of protein food on the glycosuria are observable in light or moderate cases of diabetes. Falta's observations that those protein foods which are more difficult of digestion more favorably influence the glycosuria also illustrates the difficulty of such experimentation. If the alimentary factors had been carefully controlled in these experiments it is probable that very different results would have been obtained.

In endeavoring to avoid these difficulties the depancreatinized diabetic dog also has been made use of by other workers. Unfortunately such animals are ill adapted to fine metabolic examinations of this type, for the reason that extirpation of the pancreas is followed by very severe effects, which are indeed particularly marked in case of the digestive system. It is not surprising that no certain results have been obtained by this method of experimentation. There is also considerable evidence which cannot here be detailed, to the effect that a certain amount of glucose utilization does take place locally in depancreatinized dogs in spite of data to the contrary.

Glucose formation from ingested protein has also been studied experimentally in a few isolated instances with the aid of dogs made diabetic with the use of the glucosid phlorizin. The work of Halsey,[6]

5. Von Noorden, C.: Die Zuckerkrankheit und ihre Behandlung, Berlin, 1912, Ed. 6, p. 100.

6. Halsey, J. T.: Sitzungsber d. Gesellsch. z. Beförderung d. Gesamten Wissenschaften, Marburg, 1899, p. 102.

Rohmer[7] and Bendix[8] may be referred to. The technic employed is open to various criticisms, which preclude drawing definite conclusions from this work. Reilly, Nolan and Lusk,[9] however, in two experiments were able to determine the amount of glucose formed from gelatin in metabolism.

3. DEVELOPMENT OF IMPROVED EXPERIMENTAL METHODS

As both the human diabetic and the depancreatinized dog represent serious obstacles to the successful study of glucose formation from protein, recourse was made to phlorizin diabetes. Although many experimental difficulties were encountered here also, none proved insurmountable and a technic could be developed by which the extent of protein conversion into glucose could be followed with considerable accuracy. The various details bearing on this point have been dealt with in a preceding series of articles,[10] so a repetition scarcely seems indicated. A few main points, however, may be alluded to, as the nature of phlorizin glycosuria is not so well known to many as are other forms of melituria. This kind of diabetes has been very carefully studied by Lusk and a number of other workers within recent years with the result that its metabolism is now fairly adequately understood. When phlorizin is administered to dogs in the proper manner, complete diabetes rapidly develops, the reserve of carbohydrates within the body is quickly exhausted and in the fasting state the glucose appearing in the urine bears a constant relation to the urinary nitrogen, this so-called glucose-nitrogen ratio averaging 3.4 to 1.[11] Glucose administered to such animals within certain limits is quantitatively excreted.[12] Glucose arising from nontoxic ingested substances fails to be stored up or elsewhere utilized, but appears in the urine also quantitatively. This subject has been discussed previously by the writer, who has detailed the reasons for accepting this view.[13] Recently experiments from this laboratory have been reported, which also make it very probable that all the glucose arising from protein fed to phlorizinized dogs is excreted in their urine.[14] This

7. Rohmer, P.: Ztschr. f. Biol., 1910, liv, 455.
8. Bendix, E.: Arch. f. Physiol., Supplement, 1900, 309.
9. Reilly, F. H., Nolan, F. W., and Lusk, G.: Am. Jour. Physiol., 1898, i, 405.
10. Janney, N. W.: Jour. Biol. Chem., 1915, xx, 321. Janney, N. W., and Csonka, F. A.: Ibid., xxii, 203. Janney, N. W., and Blatherwick, N. R.: Ibid., xxiii, 77.
11. The glucose-nitrogen ratio of 3.65 to 1 has been established by Lusk for the fasting phlorizinized dog and has been generally accepted. From the larger number of observations now on record, however, the slightly lower value of 3.4 to 1 has been found by Janney and Csonka to be more nearly correct.
12. Ringer, A. I.: Jour. Biol. Chem., 1912, xxii, 422.
13. Footnote 10, first reference.
14. Footnote 10, second reference.

work demonstrated that the urinary glucose and nitrogen of fasting phlorizinized animals, which quantitatively excrete ingested sugar, bear the same relation to each other as the extra glucose arising from these animals' own proteins ingested by other phlorizinized dogs does to the nitrogen contained in these proteins. In other words, just as much glucose appears in the urine after ingestion of phlorizinized dogs' proteins as is yielded by the breakdown of the fasting animals' living protoplasm. Such identical results would be impossible if all the glucose originating from the ingested proteins did not appear in the urine, for we have reason to believe that carbohydrates are not stored by fasting phlorizinized dogs (Lusk). Consequently the sugar excreted represents the maximal amount formed from the animal's body proteins.

Recently it has been shown by Sansum and Woodyatt[15] that the rise in glycosuria following ingestion of various toxic substances is not necessarily to be ascribed to sugar formation from these substances. The results obtained in the experiments to be discussed in this article are, however, not subject to this criticism, as only innocuous food substances usually representing normal constituents of animal diet were fed in this case.

In order to determine quantitatively the amount of glucose arising in diabetic metabolism from a given protein on ingestion, it is also necessary to demonstrate that at least under the experimental conditions employed complete digestion of the material fed has taken place, together with absorption and elimination of the digestive products arising from it. In this regard a variety of physiologic factors are now known to play a part. The researches of Mendel and co-workers have demonstrated that the rate and thoroughness of protein digestion is mainly dependent on the volume and texture of the material fed, as well as on the presence in the alimentary tract of other food and indigestible substances. It has also been shown that even the amount of water taken can markedly influence digestion.[16] When these factors are considered, however, digestion and absorption of proteins, whether of animal or vegetable origin, are with but few exceptions very similar.[17] These data were mostly unknown at the time when the chief part of the previous experimentation on glucose formation took place and represent an uncontrolled source of error in many of these experiments. In our preliminary studies due consideration, however, was given these physical factors. The experiments have therefore been made throughout this entire series of investigations on fasting animals and due care given to the quantity, volume and texture of the proteins fed. The

15. Sansum, W. D., and Woodyatt, R. T.: Jour. Biol. Chem., 1915, xxi, 1.
16. Bergeim, O., Rehfuss, M. E., and Hawk, P. B.: Jour. Biol. Chem., 1914, xix, 345.
17. Mendel, L. B., and Lewis, R. C.: Jour. Biol. Chem., 1913-1914, xiv, 55.

water intake was also properly regulated. In a series of preliminary control experiments the hourly nitrogen and glucose elimination were also followed and exact time limits established which insured the excretion of these products arising from the ingested proteins. It was found possible in this way so to refine the technic that the glucose arising from proteins in the metabolism of the living animal could be determined with as great degree of accuracy as accompanies certain analytic procedures.

Inasmuch as the value of many recent diabetic researches, including the present studies, depends on how directly the experimental results obtained for phlorizin diabetes are applicable to human diabetes, a few remarks relative to this subject are not out of place. As is well known, various differences exist between these two forms of glycosuria. A detailed comparison of these conditions cannot, however, be entered into in the present article. The data bearing on this subject has been collected and ably discussed by Allen,[18] to whose monograph reference may be made. The writer's standpoint concerning the nature of phlorizin glycosuria may, however, be briefly stated as follows.

Phlorizin diabetes is produced by the action of the glucosid of this name and is regarded by many to be of renal origin, in sharp distinction to diabetes mellitus. This view, however, requires modification. According to Biedl and Kolisch[19] the liver forms glucose when perfused with fluid containing phlorizin. The writer[20] has observed that the glucose content of blood to which phlorizin has been added increases on perfusion through muscle. Underhill[21] has found considerable glucose formation to take place in phlorizinized animals in which the kidney function was eliminated. It has been fully demonstrated by Lusk in various ways that the body proteins are the source of sugar excreted by fasting phlorizinized dogs. From these and further facts which could be adduced the conclusion can be drawn that phlorizin affects the tissues of the body as a whole with sugar synthesis as a result. Phlorizin diabetes is therefore to be regarded just as is diabetes mellitus, a morbid process of general nature, characterized by glucose formation from protein.

The effect of phlorizin on the kidney has been the object of many investigations. The various data and arguments on this subject also cannot here be discussed. It may be but briefly emphasized that the importance of the kidney in phlorizin diabetes, though very great, has been overestimated, for neither sugar formation in this organ nor indeed in the blood can adequately account for the production of such

18. Allen, F. M.: Glycosuria and Diabetes, Boston, 1913.
19. Biedl, A., and Kolisch, R.: Verhandl. d. 18 Cong. f. inn. Med., 1900, 573.
20. The author's unpublished experiments.
21. Underhill, F. P.: Jour. Biol. Chem., 1912, xiii, 15.

large amounts of glucose as are excreted in this form of diabetes. The local action of phlorizin on the renal organs is, however, in all probability responsible for several of the chief differences observed between this and the human form of diabetes. The hypoglycemia and various phenomena connected with glycosuria and diuresis characteristic of phlorizin diabetes are thus best explainable as the result of the toxic effect of this glucosid on the renal function.

In further comparing these two forms of diabetes the lack of the clinical symptoms of diabetes mellitus in phlorizin glycosuria cannot be fairly regarded as representing a fundamental difference for the following reason: In judging of this side of the question it must be remembered that it is difficult properly to compare the reaction of a dog subjected for a short period of time to phlorizin injections with the eminently chronic manifestations of human diabetes. Many signs of human diabetes, however, are actually to be observed in phlorizinized dogs. Such are rapid loss of weight, polyuria, and at times polyphagia, thirst, delay in the healing of wounds, and tendency to local infections. Even cataract has been noted.[22] A further discussion of this important subject cannot be entered into here. There are good grounds, however, for accepting that phlorizin diabetes has many of the characteristics which would reasonably be ascribed to diabetes mellitus of the same intensity and duration, if such an acute form of human glycosuria were known. However, no attempt to establish the identity of these conditions can be reasonably made. On the other hand, sufficient evidence, it is believed, has been advanced to show that these morbid processes are much more closely related than is generally recognized.

Aside, however, from the general nature of these two expressions of diabetes, and especially in regard to glucose formation from protein, previous studies make it very probable that this process is essentially the same in both severe human and phlorizin diabetes. Body proteins break down in either case with the liberation of nitrogen and glucose in like amounts in both these conditions.[23] Glucose formation from ingested proteins has likewise been demonstrated to take place in phlorizin as well as human diabetes. The relation of the urinary glucose to the nitrogen, or glucose-nitrogen ratio, has been repeatedly recorded as practically the same for either condition when of maximum development.[24] A human case of phlorizin diabetes showed the same glucose-nitrogen ratio.[25] It is very probable that more similarities of

22. Lusk, G.: Verbal communication to the author.
23. Footnote 10, last reference.
24. For literature see Allen, F. M., and Du Bois, E. F.: Metabolism and Treatment in Diabetes, THE ARCHIVES INT. MED., 1916, xvii, 1010.
25. Benedict, S. R., and Lewis, R. C.: Proc. Soc. Exper. Biol. and Med., 1913-1914, xi, 134.

like nature would have been brought out did human beings not present so many difficulties with regard to exact experimental study.

Granting then that the body proteins of diabetic man and the phlorizinized dog yield about the same amount of glucose in metabolism, does the same hold true for ingested proteins? We believe this is to be answered in the affirmative for the following reasons: It has been demonstrated in this laboratory[26] that very nearly the same amount of glucose was formed in phlorizinized dogs from the proteins of the living animal and from muscle protein, that is, from the chief bulk of body protein of either dog or man when fed to phlorizinized dogs. This work makes it very probable the glucose formation from proteins ingested by man is not likely to be different from that occurring in the dog, providing no fundamental differences exist in protein metabolism in general between these two species. This point is covered by the work of Osterberg and Wolf,[27] among others, who in elaborate studies could discover no salient differences between the canine and human in this respect. For these and other grounds we deem it justifiable to apply to the problems of diabetes mellitus the results of careful protein feeding experiments made on dogs having phlorizin diabetes.

4. GLUCOSE FORMATION FROM ISOLATED PROTEINS

After thus satisfying ourselves as to the reliability of the technic employed as well as to the value of the data obtained by this mode of experimentation, a representative group of chemically pure, isolated proteins was fed in a series of more than seventy metabolic experiments to diabetic dogs and the glucose yielded in the metabolism of the proteins ascertained. The proteins employed and the results obtained are shown in Table 1, which is taken from a preceding article.

TABLE 1.—GLUCOSE YIELDS OF INGESTED PROTEINS.

	Casein	Ovalbumin	Serum Albumin	Gelatin	Fibrin	Edestin (Hemp Protein)	Gliadin (Wheat Protein)	Zein (Corn Protein)
Glucose yield in per cent.	48	54	55	65	53	65	80	53

This investigation clearly established the important fact that no difference in their sugar-producing capacity exists between animal and vegetable proteins owing to their respective origins. The amount of glucose yielded in metabolism could, however, be demonstrated to vary directly with the amount of glucogenetic amino-acids contained in each

26. Footnote 10, second and third references.
27. Wolf, C. G. T., and Osterberg, E.: Biochem. Ztschr., 1911, xxxv, 329.

individual protein. Thus the wheat protein gliadin contains 43.7 per cent. glutamic acid, which is known to yield large amounts of glucose in metabolism. Gliadin yields the largest amount of glucose of all proteins hitherto examined. This is chiefly due to the large amount of this amino-acid present. Application of these new facts to the diabetic's dietary will be made in the latter part of this article.

Source of the Glucose Arising from Protein.—At various times in the medical literature discussions have arisen as to what part of the protein molecule yielded sugar, and particularly as to whether the carbohydrate content of protein could be responsible for the metabolic glucose originating from this food class. This question can, in view of the experiments just recorded, be regarded as definitely settled in the negative. Through the studies of Lusk, Dakin and others[1] it has been conclusively demonstrated that the majority of the amino-acids entering into the constitution of proteins yield glucose in metabolism. Our own work has demonstrated the fact just alluded to, that the amount of sugar so formed from proteins is dependent on the amount of glucose-yielding amino-acids entering into the make-up of each particular protein.[13] Indeed, according to recent studies in the chemistry of proteins, carbohydrate as such is present in very insignificant amounts and is to be rather regarded as an impurity than a component part of the protein molecule. This fact has been borne out by our metabolic experiments in which pure ovalbumin was fed. This protein was formerly thought to contain considerable carbohydrate, but our results show that it yields actually less glucose than various other albuminuous substances to which a carbohydrate group has never been ascribed. This is a point which seems as yet little known among authorities on diabetes. Thus von Noorden,[28] as late as 1912, believed that a carbohydrate group plays a rôle in glucose formation from protein.

5. GLUCOSE FORMATION FROM BODY PROTEINS; THE GLUCOSE-NITROGEN RATIO

The origin of the glucose excreted in diabetes has held the attention of investigators for generations. Proteins and fat are to be regarded as the chief possible sources of endogenous glucose excretion. In order to ascertain what amount of the glycosuria could be ascribed to protein and what to fat, the urinary nitrogen elimination has been studied in relation to that of sugar, that is, the glucose-nitrogen ratio. This has been done in order to determine the maximal amount of the sugar production from protein. Sugar excreted in excess of this maximum could be ascribed to fat.

---

28. Von Noorden, C.: New Aspects of Diabetes, New York, 1912. Umber, F.: Therapie d. Gegenwart, 1901, iii, 440.

But efforts to determine how much glucose can arise from protein through study of the urinary glucose-nitrogen ratio have met with many difficulties. Minkowski found that fasting depancreatinized dogs excreted glucose in relation to nitrogen as 2.8 to 1, and therefore calculated 45 per cent. as the maximal amount of body protein convertible into glucose. Lusk, using phlorizinized dogs, established the glucose-nitrogen ratio as 3.65 to 1, corresponding to a conversion of 58.5 per cent. of protein into sugar. Similar studies carried out on human diabetics have led to the vaguest results. Thus glucose-nitrogen ratios have been reported varying all the way from 0.01 to 1 to 12 to 1. Owing to this uncertainty, most authors on diabetes attach at present very little weight to the importance of the glucose-nitrogen ratio.[28] With the aid of the improved technic already alluded to, the problem of the maximal formation of glucose from protein, however, could be definitely decided. With the same precautions as previously employed in the case of isolated proteins, muscle from various species of animals was fed to phlorizin diabetic dogs and the amount of glucose arising in metabolism ascertained as hitherto. By the aid of a new analytic method[29] developed for this purpose, it became possible accurately to determine the amount of protein present in the animal muscle used in these experiments and also to ascertain the nitrogen content of this protein. By this means we were enabled not only definitely to learn how much glucose arises from muscle proteins in metabolism, but what relation this glucose actually bears to the nitrogen of the protein, that is, the real protein glucose-nitrogen ratio, which is not identical with the urinary glucose-nitrogen ratio. The protein glucose-nitrogen ratios for body proteins other than muscle were obtained in a similar manner and were found to average just about the same as in the case of the muscle proteins themselves. In this way the maximal formation of glucose from body proteins could be established by direct experiment. No great variations were found among various species as Table 5, taken from our previous studies, demonstrates. The body proteins of man were thus found to yield 58 per cent. of glucose in the diabetic metabolism, corresponding to the glucose-nitrogen ratio of 3.6 to 1.

It follows from this fact that complete diabetes in man exists when the glucose-nitrogen ratio of the urine is about 3.4 to 1 (Janney and Blatherwick). This glucose-nitrogen quotient now established as a definite value consequently becomes of importance in the study of this disease, as it represents a definite index of its severity. The nearer this ratio as exhibited by fasting diabetics approaches the value 0 to 1 the better the prognosis which may be made. Conversely the persis-

29. Janney, N. W.: Jour. Biol. Chem., 1916, xxv, 177.

tence of a high glucose-nitrogen ratio adds to the gravity with which the case is to be regarded, for not only is a maximal formation of glucose from the body proteins here taking place, but also oxidation of carbohydrates is impossible.

As a result of these studies it is also evident that the urinary ratios higher than about 3.4 to 1 previously reported for human diabetics must be based on erroneous observation. These new investigations are also applicable to the question of sugar formation from fat in diabetes as previously alluded to. Owing to the demonstration that all the glucose and no more which can originate from protein appears in the urine of severe diabetic patients and of fully phlorizinized dogs during a fast, it is evident that fat is not to be regarded as an important source of urinary glucose in diabetes. This coincides with Mandel and Lusk's[30] observations that the feeding of large quantities of fat has no influence on the sugar output of phlorizinized dogs. Though from certain fatty acids synthesis of glucose undoubtedly does occur, as has been demonstrated by Ringer and others, glucose formation from fat evidently plays no large part in the diabetic's economy. In the actual treatment of this disease it is known, however, that the addition of fats to the diet can lead to increased glycosuria and ketonuria.[31] This is, however, very probably to be regarded chiefly as a result of the stimulating action of fat on protein metabolism, for Lusk's[32] elaborate respiratory studies have demonstrated that certain intermediary products, which can also arise from fatty acids, act as a stimulus to metabolism. These facts are emphasized inasmuch as considerable doubt exists in regard to the question of sugar formation from fat.

6. GLUCOSE FORMATION FROM PROTEIN FOODS

(With the assistance of F. A. Csonka.)

Glucose Formation from Meats, etc.—The investigations just described have rendered the solution of another very practical problem possible, that is, the exact determination of the amount of glucose produced from meats and other protein foods as a result of their metabolism in the diabetic organism. The detailed results of this study are reported in this communication. Various meats were fed to dogs made completely diabetic by the use of phlorizin and the amounts of glucose arising from the food ascertained under the employment of the same technic and methods as previously employed. These experiments are accordingly not described in full. The meat was prepared for analysis and feeding by removal of all indigestible portions, ground fine in a meat grinder, the amounts for each feeding weighed, and then stewed for one hour on a steam bath. This

30. Mandel, A. R., and Lusk, G.: Jour. Am. Med. Assn., 1904, xliii, 241.
31. Allen, F. M.: Jour. Am. Med. Sc., 1915, iv, 480.
32. Lusk, G.: Jour. Biol. Chem., 1914, 1915, xx, 555.

was done with the idea of obtaining results applicable to cooked food. The eggs for analysis and feeding were hard boiled, and after removal of the shells, were passed through a meat grinder, thoroughly mixed and moistened with water before feeding. In the meat for feeding, nitrogen, total solids and, for the sake of control, the total amount of substances reducing Fehling's solution, as well as the glycogen content, were determined with employment of the same analytic methods as previously. The results of these analyses appear in Table 2.

TABLE 2.—Analysis of Meat Used in Feeding Experiments, Grams per 100 Gm. Meat *

	Total Solids	Nitrogen	Substances Reducing Fehling's Solution	Glycogen
Lean beef (first two experiments)..	25.35	3.32	0.18	Less than 0.1
Lean beef (last two experiments)...	25.08	3.28	0.18	0.08
Chicken meat.....	25.54	3.7	0.29	Less than 0.1
Fish (halibut).....	22.0	2.98	0.23	Less than 0.1
Chicken egg.....	26.9	2.1	0.31	Less than 0.1

* Analyses of rabbit meat have been published previously, Jour. Biol. Chem., 1915, xxii, 212.

The reducing substances and glycogen were present in too minute amounts to exert any obvious influence on the glucose yielded by the meat fed. This fact we have indeed demonstrated in another way. In earlier experiments muscle proteins were separated in considerable quantity from the other meat constituents and found in similar feeding experiments to give rise to precisely the same amount of glucose as did corresponding amounts of the same sample of meat previous to its being subjected to this procedure. Meat extract has also been demonstrated by Csonka[33] to be not glycogenetic, an important fact to be considered in diabetic dietetics. There is, therefore, no question but that the protein itself represents practically the entire source of the glucose derived from the meat. The meat was fed in very moderate quantities, chosen so as to administer the albuminous substances to the animals in similar amounts as our preliminary studies had demonstrated to be entirely assimilated and the products eliminated within nine hours. Meat is known to be very quickly digested, absorbed and its metabolites excreted by man and animals. Important recent studies of Mendel and Fine[34] have demonstrated that when fed in larger quantities than used in these experiments it is utilized to the extent of 100 per cent. by dogs. Lusk and his co-workers[9] have fed various amounts of meat to fasting

33. Csonka, F. A.: Jour. Biol. Chem., 1915, xx, 539.
34. Mendel, L. B., and Fine, M. S.: Jour. Biol. Chem., 1912, xi, 23.

phlorizinized dogs and demonstrated that even 500 gm. of meat is digested and eliminated as nitrogen and glucose within twelve hours after ingestion. As we have used much smaller amounts of meat and allowed twenty-four hours for elimination, there is no question as to the completeness of digestion, absorption and elimination of the digestive products formed. This is also conclusively shown by the protocols of the experiments, in which, with the exception of chicken egg, the nitrogen and glucose of the ingested material is always seen to be eliminated within twenty-four hours.

The protocols of the feeding experiments accompany this article (Table 6). For the mode of calculation of that portion of the glucose excreted which is ascribable in origin to the proteins ingested, Lusk's method, which is now generally accepted, was employed. Three or more separate experiments were performed in the case of each variety of protein food given. The results of the various experiments usually showed remarkably close agreement (see protocols). It was thus found possible to determine the extent of glucose formation from meat proteins with the same accuracy as that in the case of analytically pure proteins employed in earlier experiments.

TABLE 3.—Glucose Formed in Metabolism by Protein Foods

Food	From Raw Material, per Cent.	From Water-Free Material, per Cent.
Beef	9.5	38
Rabbit	11	45
Fish (halibut)	12	45
Chicken	12	48
Chicken egg	9.5	36

In Table 3 are recorded the average results of the feeding experiments given in detail in the protocols. It is seen that the amounts of glucose produced from the meats of various origin show no more deviation than might be ascribed to experimental error. These results stand therefore in accord with data previously obtained in this laboratory, which showed that the body proteins of various species of animals all yield approximately like amounts of glucose in metabolism (Janney and Blatherwick).

The reliability of these results for the various meats studied we believe to be scarcely open to question, owing to the careful preliminary experiments alluded to. The same cannot, however, be maintained for the egg experiments, in which larger amounts of material were fed than our later control experiments referred to above. Owing

principally to this fact, in all likelihood a much longer time was required for the sugar and nitrogen arising from them to be excreted than in the case of the meats. The results obtained in this case are perhaps not so dependable as in the meat experiments. They are, however, very regular and do not vary more than the similarly obtained glucose values of the other protein foods. On these grounds they are included with this explanation in our report.

TABLE 4.—GLUCOSE FORMATION FROM PROTEIN FOOD; COMPARATIVE TABLE

	Water Content, per Cent.	Glucose Yield, per Cent.	Amount Equivalent to 100 Gm. Bread, Gm.	Calories per 100 Gm.
Beef, raw	74.8	9.5	642	150
Beef, broiled	54 †	17.5	348	208
Beef, dried or smoked	54.3	21	290	185
Beef, canned or corned	51.8	18.2	335	270
Beef, roasted	48.2	19.5	313	241
Chicken meat, raw	74.5	12	508	197
Chicken meat, roasted	59.9	19.2	317	245
Rabbit, raw	74.7	11	555	...
Rabbit, broiled	61.4†	16.8	363	...
Halibut steak, raw	75.4	12	508	124
Halibut steak, fried	54.2†	22.3	255	173
Eggs, raw	73.7	10.3	592	153
Eggs, boiled	73.2	10.51	580	166
Eggs, fried	70.4†	11.6	526	160
Ovalbumin*	....	54	113	...
Gelatin*	....	65	94	366
Casein*	....	48	127	...
Corn protein, zein*	....	53	115	...
Wheat protein, gliadin*	....	80	76	...
Flour*	....	92.5	...	...
Bread	34 ‡	61	...	277

* Calculation based on water-free material.
† Writers' analysis.
‡ Analyses from Conn. Agric. Exper. Station Report, Sec. 1, Diabetic Foods, 1913.

The results of this series of protein food experiments, though obtained at the cost of considerable effort, are not directly applicable as they stand, however, to the problems of the diabetic's dietary. This is true as they are referable as calculated to raw material, except in the case of the egg feeding. By taking into consideration the loss of water in cooking, it is possible, however, to compute the amount of

glucose which arises in the metabolism of such protein food as served. Such calculations have been made and appear in Table 4. As about one third of the water is usually lost in the culinary preparation, the glucose yields are correspondingly increased. It is apparent that a very considerable amount of glucose arises from meats. Owing chiefly to their higher water content raw, boiled or fried eggs produce but slightly more than one half the sugar which is formed from roast meat. Eggs are therefore to be regarded as a standard article of the diabetic's protein dietary. This experimental observation coincides with the experience of von Noorden with the human diabetic, as this clinician is accustomed to feed eggs in preference to other protein food in order to obtain a decrease in the glycosuria.

In the dietary tables for diabetics compiled by Carl von Noorden various foods are compared in regard to their carbohydrate content to white bread and equivalent values calculated. This method of comparison, as the present article demonstrates, is a rather inexact one, for the additional glucose formed within the organism from the proteins of the foods was not taken into account. In order then to supply a more proper basis for comparison of such foods from this standpoint it is necessary to ascertain the amount of sugar actually arising in the metabolism of bread. To accomplish this a final series of experiments was carried out, some of which have been reported in detail by Mr. Csonka[35] from another point of view. On account of its more constant constitution in these experiments, wheat flour was used in preference to bread. The same method of experimentation was employed as previously, with satisfactory results. It could thus be ascertained that flour produced an amount of glucose in metabolism equivalent to 92.5 per cent. of its water-free weight. From the data so obtained it is possible to calculate that the amount of glucose formed from bread in metabolism is about 61 per cent.

We were now finally in a position to calculate the amounts of protein food equivalent from the standpoint of actual glucose formation in the body to bread. These values appear in the last column of Table 4. It is seen that about from 3 to 3.5 parts of cooked meats correspond to one part wheat bread. In view of this fact it follows that rather more care in regard to the protein part of the diabetic's dietary should be exercised than is at present usually deemed necessary. In order to emphasize the marked glycogenetic property of proteins the bread equivalents of various food proteins have been added. Thus gelatin, recommended by von Noorden as a permissible food, produces 65 per cent. glucose within the body, and but 94 parts of gelatin are equivalent to 100 parts of bread. It must be remembered, however,

35. Csonka, F. A.: Jour. Biol. Chem., 1916, xxvi, 327.

that gelatin is eaten in the form of a jelly with a corresponding resulting reduction of the percentage of metabolic glucose formed from it. It is nevertheless certainly no longer to be regarded as a proper food for diabetics.

With regard to the relative usefulness of the various kinds of bread in the diabetic's dietary, the following may here be observed. As nearly as can be at present approximated, the proteins of corn bread yield about 50 per cent. of glucose in metabolism, wheat and rye bread about 66 per cent. The results of the average analyses of Atwater and Bryant are, respectively, for graham (wheat), corn and rye bread, protein, 8.9, 7.9, 11.9 per cent.; carbohydrates, 52.1, 46.3, 35.9 per cent. From this and other data in this article the total percentile sugar yield of these important foodstuffs in metabolism may be estimated as follows: white wheat bread 61, graham wheat 55, corn 50 and rye 44 per cent. From these data it would seem as if rye bread should be preferred for diabetic use. Aside, however, from the fact that Americans as a rule do not relish rye bread, its caloric value is but three fourths that of the other varieties mentioned. Everything considered, then, it seems evident that white wheat bread is least desirable for the diabetic's use, corn bread and other corn-meal preparations most desirable, graham and rye bread occupying a middle position.

7. GLUCOSE FORMATION FROM PROPRIETARY FOODS

So much emphasis has been laid by the physician on the necessity of excluding carbohydrates from the diet of the glycosuric patient that this has become the aim of the manufacturers in preparing diabetic foods. Indeed, it still remains the custom of physicians to recommend at times such special breads and other products on account of their high protein and low carbohydrate content. Many falsifications and misleading statements in regard to the makeup of these foods have, however, been made on the part of their promoters. Analyses of such American commercial products by the state agricultural experiment stations, of German preparations by Magnus-Levy,[36] Janney[37] and others have already called sufficient attention to such misrepresentations. A study of the actual nutritive value of these preparations to the diabetic, however, is of more importance than the claims made for them commercially. It has been found possible to apply the experimental data previously obtained to these patent diabetic foods and thus to secure a knowledge of their real usefulness to the glycosuric patient. The results of this consideration are collected in Table 5.

36. Magnus-Levy, A.: Berl. klin. Wchnschr., 1910, xlvii, 233.
37. Janney, N. W.: München. med. Wchnschr., 1910, lvii, 2086.

The protein and carbohydrate values used in making these calculations are those compiled by the Connecticut Agricultural Experiment Station[38] from scientific investigations of these food products and are said to be regarded as reliable. The percentile amount of glucose produced in the body by these products (third column, Table 5) has been calculated by adding to their carbohydrate content the amount of glucose formed from the protein present, these latter values being taken from our experiments. It has been previously ascertained by the author that casein produces 48 per cent. of glucose. For plasmon and sanatogen, which are casein preparations, this value has accordingly been utilized.

TABLE 5.—GLUCOSE FORMATION FROM PATENT DIABETIC FOODS

	Protein, per Cent.	Carbohydrate, per Cent.	Glucose Yield in Metabolism, per Cent.	Amount Equivalent to 100 Gm. Bread, Gm.
Gildine, Menley & James, New York	91.4	1	66	92
Sanatogen, Bauer Chem. Co., Berlin	80.1	4.2	61	100
Plasmon, Plasmon Co., London	78.7	0	56	109
Diabetic Biscuit, Johnson Educ. Food Co., Boston	25.2	59	77	79
40 % Gluten Biscuit, Kellogg Food Co., Mich.	35.8	54	79	77
80 % Gluten Biscuit, Kellogg Food Co., Mich.	82.4	4.4	68	97

In order to ascertain the total amount of sugar derivable from gluten preparations, it is necessary to ascertain the amount of glucose arising from the wheat proteins. This was done as follows: Of the wheat proteins about 90 per cent. are represented by glutelin and gliadin in the proportion of 10 to 8.4. These two proteins are the chief constituents of gluten. In the absence of actual feeding experiments the amount of metabolic glucose derived from glutelin was calculated as previously done in the case of other proteins, from the amounts of glycogenetic amino-acids obtained from it by hydrolysis.[27] The resulting value is 66.3 per cent. Gliadin produces 80 per cent. of glucose in metabolism, as determined experimentally. Accepting that the remaining proteins of the wheat gluten yield about 60 per cent. of glucose under the same circumstances, we can calculate from these data that the wheat gluten gives rise to about 70.5 per cent. of glucose in metabolism. This value has been made use of in compiling the table. It must be borne in mind that the values so calculated are only approximate, owing to the manner in which they are obtained. Thus the method commonly in use for estimating the amount of protein

38. Diabetic Foods, Conn. Agr. Exper. Station, Annual Report, 1913, i, 1.

present in albuminous foods is quite inaccurate. Attention to this has been recently called by the writer.[39] Table 5, however, serves forcibly to illustrate the lack of value or indeed positive harmfulness of such commercial products when eaten by the diabetic. It may be remarked that sanatogen, plasmon and glidin, the last a German product identical to that appearing in Table 5, are recommended by von Noorden among foods permissible to all diabetic patients.[40]

A further important fact is also brought out by the data of Table 5. Contrary to the prevailing opinion, the use of food preparations with a high protein and a low carbohydrate content is of not much more advantage to the diabetic than that of others containing much more carbohydrate and less protein. This is well illustrated by comparing the Kellogg Food Company's 40 per cent. gluten biscuit with their 80 per cent. product. Although in the second case the protein has been increased from 35.8 to 82.4 per cent. and the carbohydrates decreased from 54 per cent. to 4.4 per cent., the glucose formed in the metabolism of this product could thereby be reduced from 77 to only 58 per cent. The chief lesson to be drawn from these considerations is obvious. Food products containing high amounts of proteins cannot be properly recommended for the use of diabetics, inasmuch as most of them present no advantages over wheat bread fed in like amount. As these articles are with few exceptions relatively very expensive, and, owing to advertising propaganda, the unsuspecting diabetic is often deluded as to their value, their sale should no longer be encouraged by either physician or layman. A comprehensive list of such diabetic foods has been published, with their protein and carbohydrate content, by the Connecticut Agricultural Experimental Station.[28] This may be referred to for determining the utility of diabetic foods other than the few examples quoted in this article.

8. APPLICATION OF RESULTS TO THE DIABETIC DIETARY

The experimental results described in this article were obtained with the aid of the same technic throughout. Optimal conditions for digestion and absorption were maintained for small amounts of protein foods in highly assimilable form which were fed to fasting subjects. Reasons have already been stated for regarding the glucose values as representing the maximal sugar formation from the protein material in each case. It is therefore justifiable to regard the tables given as a general index of the utility of proteins and protein food for the diabetic and to draw comparative conclusions from these data as has been done in the foregoing pages.

39. Janney, N. W.: Proc. Soc. Exper. Biol. and Med., 1916, xiii, 83.
40. Von Noorden, C.: Die Zuckerkrankheit und ihre Behandlung, Berlin, 1912, Ed. 6, appended tables.

In actual practice, however, such ideal conditions as the experimental do not exist. The various factors influencing the extent and rate of protein assimilation here become of decided consequence. Among them are the texture of the food served, thoroughness of mastication, presence of substances other than protein in the diet, volume of indigestible material in the intestinal tract, variations in the tolerance to carbohydrates, the effect of exercise and psychic influences. On applying, then, to the diabetic's dietary the results of the researches described in this article, the influence exerted by these factors must be regarded. A very palatable and digestible protein food, though shown to yield much more glucose by our experiments than another example, may possibly, through poorer digestibility and absorption or the fact that these processes take place more slowly in this case, be the cause of less sugar excretion than the second food on their administration to patients. Von Noorden's view that vegetable proteins more favorably influence the glycosuria than does meat, though based on insufficient experimental proof, is, however, susceptible of explanation on these grounds. Vegetable proteins, as we have seen, actually form as much, and in some instances more, glucose in metabolism than do meats, when both these forms of food are fed under optimal conditions. If, however, vegetables are for any reason eaten by diabetics in a form less or more slowly assimilable than a given amount of meat, glucose formation would be correspondingly decreased in the former case. Further exact experiments seem here indicated.

The aim of modern cooking, however, is to render all food, whether animal or vegetable, highly palatable and digestible. The alimentary factors alluded to play in better practice not so great a rôle as might be supposed. With some possible exceptions, these variables would, especially in better households, tend to exert a more similar influence on the course of protein digestion. For this reason the glucose values of the tables in this article are believed to be applicable to the human dietary in a comparative way, even though they may not always represent the precise extent of glucose formation under the special conditions prevailing at the time of their ingestion. Thus, protein foods *A* and *B* may be equivalent to 80 and 60 gm. of bread, respectively, as experimentally determined. Being eaten under mutually the same but less favorable alimentary conditions by a diabetic, each protein might undergo 90 per cent. absorption. Therefore the values in the tables still remain criteria of the relative utility of these proteins. It is to be emphasized, however, that the results of the series of experiments here reported are to be regarded merely as a general gage of the relative adaptability of protein foods to the diabetic dietary.

The Choice of Diet for Diabetics.—The experimental data described in this communication emphasize the fact that large quantities of glu-

TABLE 6.—Protocols of Feeding Experiments

Protein Food Administered		Nitrogen Fed, Gm.	Weight of Dog, Gm.	Period, Hr.	Urinary Nitrogen, Gm.	Urinary Glucose, Gm.	G:N	Extra Glucose	
Kind	Amt., Gm.							Amt., Gm.	In Terms of Material Fed, %
Lean beef	50	1.66	9.95	24 24 24 24	9.23 9.12 8.64 6.87	32.64 34.9 29.1 22.22	3.54 3.83 3.37 3.23	4.46	8.92
Lean beef	35	1.16	7	24 24 24	8.58 5.87 8.19	31.8 20.7 25.6	3.7 3.53 3.13	3.3	9.43
Lean beef	89.6	2.84	8.6	24 24 24	8.18 8.98 7.38	26.79 28.17 23.57	3.28 3.13 3.19	8.34	9.30
Lean beef	108.02	3.5	7	24 24 24 24 24 24	5.77 5.23 4.84 4.76 6.79 4.2	18.64 16.85 16.26 14.24 20.39 13.86	3.23 3.24 3.36 2.99 3.01 3.3	9.57	8.86
Lean beef	91.67	2.97	9.9	24 24 24	8.03 9.88 7.71	29.23 34.63 27.42	3.64 3.47 3.55	9.89	10.79
Chicken meat	134.85	5	10	12 12 24 24	5.12 4.77 10.89 7.76	16.78 14.52 37.78 24.75	3.28 3.05 3.47 3.19	19.14	14.2
Chicken meat	128.1	4.75	9.1	24	9.19	28.25	3.07	14.23	11.1
Chicken meat	82.93	3.07	6.1	12 12 24 24	3.89 5.74 8.44 5.57	15.27 19.31 28.73 18.18	3.92 3.37 3.4 3.27	10.91	11.86
Chicken meat	74.16	2.75	5.9	24 24	6.27 4.4	21.43 15.55	3.42 3.53	9.48	12.79
Chicken meat	74.16	2.75	5.5	24 24	5.98 3.69	19.12 12.5	3.2 3.39	7.98	10.76
Halibut	167.8	5	10	12 12 24	4.77 4.16 11.23	16.26 14.03 37.04	3.41 3.37 3.3	15.92	9.49
Halibut	143.1	4.25	8.5	24 24 24	2.67 10.26 7.19	8.03 31.71 21.58	3.01 3.09 3	13.64	9.54
Halibut	63.97	1.9	3.8	24 24 24	3.49 4.73 3.75	10.92 15.43 11.56	3.13 3.26 3.09	6.6	10.33
Chicken egg	176.2	3.7	7.4	12 12 24 12 12	4.41 3.92 10.5 3.95 4.31	16.95 15.75 40.28 16.95 16.05	3.85 4.02 3.83 4.29 3.73	16.04	9.11
Chicken egg	154.8	3.25	6.5	24 24 12 12	7.82 8.44 3.31 3.07	27.55 31.25 12.66 10.75	3.52 3.7 3.85 3.5	10.1	9.11
Chicken egg	390.4	8.3	16.4	24 12 24 12	12.49 5.53 15.6 4.8	40.82 21.05 61.21 20.13	3.3 3.8 3.93 4.28	40.76	10.44

* For protocols of rabbit experiments see Janney, N. W., and Csonka, F. A.: Jour. Biol. Chem., 1915, xxii, 203.

cose are formed within the diabetic organism from food proteins. Evidently the classic severe or strict diet, consisting chiefly of protein, still represents large quantities of sugar-forming material, however carefully carbohydrates are excluded from the articles consumed in such food. It seems, in view of these new results, scarcely a wise procedure to strive to eliminate every gram of carbohydrate from such a diet, inasmuch as nearly two thirds of the proteins fed are found to be converted into glucose in course of metabolism by the diabetic. As it is a matter of clinical experience that large quantities of fats serve to increase both glycosuria and ketonuria, it may be fairly asked what then remains for the diabetic to eat if protein, carbohydrates and fats all contribute to increase the amount of sugar lost to the body in the urine.

This question has indeed been logically answered by Allen, whose well-known treatment has emphasized the good results to be obtained from a complete fast. The rationale of the Allen treatment becomes more evident when one is mindful of the fact that not carbohydrates alone, but all the three great classes of foodstuffs may give rise to increased glucose formation. Thus it becomes apparent that only by total exclusion of all food, a complete rest can be given to the sugar utilizing function of the organism.

The diabetic, however, can not refrain indefinitely from food. How then feed him? In view of the series of experiments here reported it is likely that a diet containing moderate amounts of protein and fat and low amounts of carbohydrate is after all the most judicious one to be employed. It seems that only by very discriminatingly balancing the various advantages and disadvantages of each kind of foodstuff can the proper quantity for a given case be best determined. With the use of the food table giving the equivalents of meats and bread, the amount of protein food in relation to carbohydrates can be easily calculated.

9. SUMMARY

A critical study of diabetes mellitus and phlorizin diabetes has led to the conclusion that glucose formation from protein in both these conditions is essentially the same. It is therefore justifiable to apply the very much more accurate results which can be obtained in phlorizin experiments to the study of human diabetes. By employing a carefully controlled technic it was found possible to quantitatively determine the amount of glucose formed in the organism from ingested proteins. The chief results of previous investigations of the writer and co-workers are collected. They are as follows: Isolated proteins were found to yield large amounts of glucose in metabolism, varying from 48 to 80 per cent. according to the protein examined. Contrary to existing opinions, the animal or vegetable origin of proteins bears no

relationship to their ability to produce glucose in the animal organism, this function being found to be mainly dependent on the amounts of sugar-yielding amino-acids entering into the constitution of these various proteins.

The formation of glucose from body proteins was also studied. It could be shown that body proteins of man and animals yield about 58 per cent. of glucose in metabolism. The nitrogen of these proteins bears about the relation of 3.6 to 1 to the glucose formed from them. This definite establishment of the glucose-nitrogen ratio is of value in the prognosis of diabetes. Cases showing such a high urinary glucose-nitrogen ratio, average 3.4 to 1, are to be regarded as grave. The lower the ratio the more favorable is the prognosis. As the glucose excreted by the fasting diabetic is of protein origin, sugar formation from fat does not take place to any great extent in this disease.

New experiments relative to glucose formation from protein foods are also reported. The amount of glucose originating in the diabetic metabolism from various meats was ascertained with use of the same technic as hitherto. In von Noorden's food tables for diabetics, glucose formation from protein has not been taken into account. By adding the amounts of glucose yielded in metabolism by the proteins of a given food to its carbohydrate content it is possible, however, to ascertain the actual amount of sugar, both set free and formed in the metabolism of such foods. A more accurate table could thus be constructed showing the relative adaptability of protein foods to the diabetic dietary, as compared to equivalent amounts of bread. Finally, various proprietary protein foods were studied in like manner. It was found that such preparations present no advantages over equal amounts of bread when fed to diabetics, as the large amount of protein present leads to the formation of considerable glucose in metabolism.

SOME STUDIES OF A DIURETIC (THEOCIN) *

HENRY A. CHRISTIAN, M.D.
BOSTON

In 1913 and 1914 there were published by myself and my associates[1] several studies of the action of diuretics on animals with acute experimental renal lesions. In general, these studies showed that diuretics in acute experimental nephritis were ineffectual or injurious, very often the latter. In 1915 a brief report[2] was made of observations on the effect of diuretic drugs in patients with chronic nephritis. In a recent Harvey Lecture[3] this same subject is touched on. Here it is pointed out that frequently when the kidney is damaged diuretics do not cause a diuresis, or if a diuresis occurs, there may be evidence of marked renal fatigue subsequent to the diuresis. Skepticism has been expressed as to the efficacy of diuretic drugs in cases of nephritis in which the kidney is seriously damaged. In these several studies theocin was used, as well as other diuretics.

During the past winter further study has been made of the action of theocin in patients with acute or chronic nephritis admitted to the medical wards of the Peter Bent Brigham Hospital. The general plan of this study was first to investigate the patients by the usual methods of physical examination, next to study their renal function by several methods and then to place them on a fixed diet for several days preceding and following one or several doses of theocin. During this latter period some patients had the sodium chlorid and nitrogen determined quantitatively in the twenty-four hour amount of urine; in other patients these quantifications were made in two-hour portions of day

* Submitted for publication June 12, 1916.
* From the Medical Clinic of the Peter Bent Brigham Hospital.
* Read at the meeting of the Association of American Physicians, held in Washington, D. C., May 11, 1916.

1. Christian: Diuretic Drugs in Acute Experimental Nephritis, Jour. Am. Med. Assn., 1913, lxi, 267. Christian and O'Hare: A Study of the Therapeutic Value of a Diuretic (Theobromin Sodium Salicylate) in Acute Experimental Nephritis, THE ARCH. INT. MED., 1913, xi, 517. Walker and Dawson: The Effect of Diuretic Drugs on the Life of Animals with Severe Acute Nephritis, ibid., xii, 171. Christian: The Effect of Theobromin Sodium Salicylate in Acute Experimental Nephritis as Measured by the Excretion of Phenolsulphonephthalein, ibid., 1914, xiv, 829. Fitz: The Immediate Effect of Repeated Doses of Theobromin Sodium Salicylate and Theocin on Renal Function in Acute Experimental Nephritis, ibid., 1914, xiii, 945.

2. Christian, Frothingham, O'Hare and Woods: Am. Jour. Med. Sc., 1915, cl, 666.

3. Christian: Am. Jour. Med. Sc., 1916, cli, 625.

urine and one portion of night urine.† Following the giving of theocin, certain tests of renal function were repeated and contrasted in result with similar tests before the theocin was given. Three types of cases were studied: patients with acute nephritis, patients with chronic nephritis and patients with chronic cardiorenal disease.

ACUTE NEPHRITIS

Case 1 (P. B. B. H. Med. No. 4159).—A man, aged 27, was admitted to the hospital Feb. 14, 1916, with a diagnosis of acute nephritis. His symptoms had lasted one week, developing one and one-half weeks after a sore throat and cold in the head lasting four days. He suffered from headache and slight edema of the eyelids and feet. There was no edema at the time of the tests. The blood pressure on February 14 was systolic 144, diastolic 100; on the 18th, systolic 140, diastolic 92; on the 22d, systolic 120, diastolic 88; and on the 26th, systolic 112, diastolic 80.

A Wassermann reaction on the blood serum proved negative. Examination of the urine on February 14 showed a trace of albumin and many granular casts and leukocytes. On February 26 there was no albumin, no casts, and only an occasional leukocyte. Phenolsulphonephthalein excretion on February 15 was 60 per cent. in two hours. The blood urea nitrogen on February 15 was 11.25 mg. per 100 c.c. of blood; on the 24th it was 17.5 mg., and on the 28th, 18.5 mg. The index of urea excretion (McLean) on February 24 was 129 per cent., and on the 28th, 71.5 per cent.

TABLE 1.—Analyses of Twenty-Four Hour Amount of Urine

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
2/21-22	530	1.025	0.74	3.92	0.24	1.27
2/22-23	220	1.025	1	2.2	0.35	1.12
2/23-24	475	1.023	0.92	4.37	0.45	2.14
2/24-25	782	1.018	0.66	5.16	0.34	2.66
On February 25 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
2/25-26	1,360	1.014	0.4	5.44	0.31	4.22
2/26-27	280	1.024	1.11	4.22	0.34	1.32
2/27-28	633	1.014	0.58	3.67	0.25	1.58

The diet was approximately 25 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000.

Figure 1 illustrates graphically the daily variations of the amount of urine and the total nitrogen and sodium chlorid, as well as the specific gravity and the percentage concentration of sodium chlorid and nitrogen, with the of three doses of 0.1 gm. each of theocin on one day of the observation. Table 1 gives the results of the urinary analyses.

† It is a pleasure to acknowledge the assistance of Miss Russel and Miss Cate, chemical technicians, in making these numerous quantitations of sodium chlorid and nitrogen.

Case 2 (P. B. B. H. Med. No. 4245).—A man, aged 45, was admitted to the hospital Feb. 28, 1916, with a diagnosis of acute nephritis. His symptoms had lasted one week, beginning with a cold, lacrimation, headache, slight hacking cough, chilly feelings and pains in the chest. The patient had on entrance no other symptoms except those described above as associated with the onset. Coming to the outdoor department for this condition, he was examined and it was found that he had albumin in his urine and enormous numbers of casts of all varieties. The blood pressure on February 29 was systolic 108, diastolic 62; on the 12th, systolic 120, diastolic 70; on the 24th, systolic 138, diastolic 78; and on April 5, systolic 115, diastolic 82.

A Wasserman reaction on the blood serum proved negative. The urine on February 29 showed a slight trace of albumin and enormous numbers of finely and coarsely granular and hyaline casts, some with epithelial and red blood cells attached. On April 7 there was the slightest possible trace of albumin, no casts, and only an occasional epithelial cell. The phenolsulphonephthalein excretion on February 29 was 50 per cent. in two hours, and on March 18, 45 per cent. in two hours. The blood urea nitrogen on March 1 was 47.5 mg. per 100 c.c. of blood; on the 7th, 13.75 mg.; on the 10th, 12.25 mg.; and on April 10, 17.62 mg. per 100 c.c. of blood. The index of urea excretion (McLean) on March 1 was 35 per cent.; on the 7th, 118 per cent.; on the 10th, 89 per cent., and on April 7, 69 per cent.

TABLE 2.—Analyses of Twenty-Four Hour Amount of Urine

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/ 2/16	810	1.023	1.72	13.93	0.03	0.24
3/ 3/16	472	1.025	1.26	5.96	0.03	0.14
3/ 5/16*	524	1.022	1.18	6.19	0.11	0.58
3/ 6/16	615	1.020	1.1	6.77	0.19	1.17
3/ 7/16	980	1.014	0.44	4.31	0.26	2.55
On March 8 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
3/ 8/16	900	1.011	0.41	3.69	0.24	2.16
3/ 9/16	300	1.016	0.56	1.68	0.13	0.39
3/10/16	200 lost 829	1.013	0.5	4.15	0.16	1.32
3/11/16	1,225	1.011	0.37	4.53	0.23	2.81
3/12/16	620	1.020	0.82	5.08	0.34	2.11

* The urine for March 4 was discarded because it had been left in a warm room for twenty-four hours.

The diet was approximately 25 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000.

Figure 2 illustrates graphically the daily variations as in Figure 1. Table 2 gives the urinary findings.

Case 3 (P. B. B. H. Med. No. 4261).—A man, aged 32, was admitted to the hospital March 1, 1916, with a diagnosis of acute nephritis. The symptoms had lasted ten days, developing one month after a tonsillitis with a peritonsillar abscess, followed by pain in some of the patient's joints. There had been slight edema of the face and legs, but there was none at times of tests. The blood pressure on March 4 was systolic 122, diastolic 85; on the 20th, systolic 140,

diastolic 90; on April 9, systolic 128, diastolic 88; and on April 21, systolic 125, diastolic 82.

A Wassermann reaction on the blood serum was negative. The urine on March 2 showed a large trace of albumin and very many red blood cells. On April 28 there was a slight trace of albumin and a moderate number of fine and coarsely granular casts, an occasional cellular cast and epithelial and white blood cell. The phenolsulphonephthalein excretion on March 2 was 36 per cent. in two hours; on April 6, 11 per cent. in two hours, and on April 28, 24 per cent. in two hours. The blood urea nitrogen on March 7 was 45 mg. per 100 c.c. blood; on the 10th, 50.62 mg. per 100 c.c. blood, and on the 28th, 59.37 mg. per 100 c.c. blood. The index of urea excretion (McLean) on March 7 was 3.12 per cent.; on the 10th, 2.48 per cent., and on April 28 it was 7.55 per cent.

TABLE 3.—Analyses of Twenty-Four Hour Amount of Urine

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/ 2/16	956	1.014	0.43	4.12	0.5	4.79
3/ 3/16	168	1.015	0.22	0.37	0.31	0.52
3/ 5/16*	715	1.011	0.21	1.5	0.2	1.43
3/ 6/16	720	1.011	0.37	2.66	0.18	1.3
3/ 7/16	825	1.012	0.21	1.75	0.17	1.42
On March 8 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
3/ 8/16	1,162	1.010	0.31	3.6	0.21	2.44
3/ 9/16	845	1.010	0.3	2.54	0.15	1.27
3/10/16	918	1.011	0.32	2.94	0.17	1.56
3/11/16	820	1.012	0.31	2.54	0.2	1.64
3/12/16	740	1.012	0.38	2.81	0.19	1.41

* The portion of urine for March 4 was discarded because it had been left in a warm room twenty-four hours.

The diet was approximately 25 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000.

Figure 3 illustrates graphically the daily variations as in Figure 1. Table 3 gives the urinary findings.

Case 4 (P. B. B. H. Med. No. 4273).—A man, aged 21, was admitted to the hospital March 3, 1916, with a diagnosis of acute nephritis. The trouble had lasted one week, developing after an infection in the right forefinger and thumb. There was slight headache, backache and slight swelling of the ankles, but there was no edema at times of tests. The blood pressure on March 4 was systolic 160, diastolic 90; on the 12th, systolic 130, diastolic 80; on the 24th, systolic 110, diastolic 75; and on April 5, systolic 112, diastolic 68.

A Wassermann reaction on the blood serum was negative. The urine on March 4 showed a trace of albumin, rare granular casts, many red and many white blood cells. On April 7 there was a very rarely granular cast, and an occasional epithelial cell. The phenolsulphonephthalein excretion on March 5 was 50 per cent. in two hours. The blood urea nitrogen on March 11 was 8 mg. per 100 c.c. of blood; on the 20th, 9.75; on the 23d, 11.37; and on April 7, 12.62 mg. per 100 c.c. of blood. The index of urea excretion (McLean) on March 11 was 93.5 per cent.; on the 20th, 71.5 per cent.; on the 23d, 114.0 per cent; and on April 7, 168.0 per cent.

The diet from March 17 to 23 was approximately 25 gm. protein, 4 gm. sodium chlorid and total calories 2,000. From March 23 to 25 it was approximately 75 gm. protein, 4 gm. sodium chlorid and total calories 2,000.

Figure 4 illustrates graphically the daily variations as in Figure 1. Table 4 gives the urinary findings.

TABLE 4.—Analyses of Twenty-Four Hour Amount of Urine

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/17/16	800	1.013	0.42	3.74	0.18	1.6
3/18/16	1,060	1.012	0.56	5.96	0.15	1.58
3/19/16	920	1.015	0.51	4.69	0.16	1.48
3/20/16	1,358	1.009	0.37	5.03	0.12	1.63
On March 21 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
3/21/16	1,725	1.008	0.22	3.8	0.14	2.42
3/22/16	915	1.012	0.43	4.49	0.12	1.1
3/23/16	1,317	1.012	0.42	5.51	0.09	1.19
3/24/16	1,317	1.014	0.57	7.51	0.15	1.98
3/25/16	870	1.017	0.74	6.44	0.18	1.56

TABLE 5.—Analyses of Twenty-Four Hour Amount of Urine

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/28/16	533	1.029	1.35	7.47	0.24	1.33
3/29/16	590	1.019	1.38	8.14	0.15	0.89
3/30/16	398	1.019	1.3	5.17	0.11	0.44
3/31/16	286	1.020	1.14	4.4	0.12	0.46
On April 1 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
4/ 1/16	598	1.020	1.06	6.25	0.22	1.36
4/ 2/16	220	1.020	1.08	2.47	0.24	0.77
4/ 3/16	332	1.022	1.07	3.55	0.66	2.26
4/ 4/16	400	1.023	1.23	4.88	0.17	0.68
4/ 5/16	345	1.020	1	3.45	0.16	0.55

Case 5 (P. B. B. H. Med. No. 4383).—A man, aged 32, was admitted to the hospital March 23, 1916, with a diagnosis of acute nephritis. The symptoms had lasted two weeks, following a moderately severe cold. There was dark urine with some scalding on urination. There was no edema at the time of the tests. The blood pressure on March 23 was systolic 128, diastolic 85; on April 1,

systolic 110, diastolic 70; on April 5, systolic 120, diastolic 78; and on April 13, systolic 110, diastolic 70.

A Wassermann reaction on the blood serum was negative. The urine on March 23 showed a large trace of albumin and many hyaline and finely granular casts, and but few red blood cells and leukocytes. On April 14 there was a slight trace of albumin, and an occasional granular cast, leukocyte and epithelial cell. The phenolsulphonephthalein excretion on March 28 was 39 per cent. in two hours, and on the 31st, 55 per cent. in two hours. The blood urea nitrogen on March 31 was 19.43 mg. per 100 c.c. blood, and on April 3, 14.68 mg. The index of urea excretion (McLean) on March 31 was 78 per cent., and on April 3, 95.2 per cent.

The diet was approximately 25 gm. protein, 4 gm. sodium chlorid and total calories 2,000. Table 5 gives the urinary findings.

CASE 6 (P. B. B. H. Med. No. 4314)—A man, age 31, was admitted to the hospital March 13, 1916, with a diagnosis of acute nephritis. The symptoms had existed four days without any history of antecedent infection, but with evident caries of teeth. There were severe headache, edema of the face, high-colored urine and chilly sensations, but there was no edema at the time of the tests. The blood pressure on March 13 was systolic 120, diastolic 90; on the 20th, systolic 108, diastolic 60; on the 28th, systolic 108, diastolic 60; and on April 5, systolic 110, diastolic 60.

TABLE 6.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/28/16	1,115	1.018	0.87	9.7	0.31	3.46
3/29/16	1,210	1.015	0.76	9.2	0.24	2.9
3/30/16	940	1.017	0.5	4.7	0.44	4.14
3/31/16	820	1.019	0.98	8.13	0.22	1.82
On April 1 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
4/ 1/16	1,340	1.017	0.71	9.51	0.26	2.48
4/ 2/16	1,122	1.016	0.63	7.07	0.13	1.46
4/ 3/16	770	1.018	1.28	9.86	0.12	0.92
4/ 4/16	1,352	1.015	0.58	7.57	0.22	2.97
4/ 5/16	900	1.014	0.64	5.76	0.13	1.17

A Wassermann reaction on the blood serum was negative. The urine on March 14 showed a very slight trace of albumin, many coarsely granular casts, epithelial cells and leukocytes, and an occasional red blood cell. On April 8 there was no albumin and but few epithelial cells and leukocytes. The phenolsulphonephthalein excretion on March 14 was 56 per cent. in two hours, and on March 31, 64 per cent. in two hours. The blood urea nitrogen on March 15 was 20 mg. per 100 c.c. blood; on the 31st, 15.126 mg., and on April 3, 10.75 mg. The index of urea excretion (McLean) on March 15 was 208 per cent.; on the 31st, 192 per cent., and on April 3, 267 per cent.

The diet was approximately 75 gm. protein, 4 gm. sodium chlorid and total calories 2,000. Table 6 gives the urinary findings.

SUMMARY OF CASES OF ACUTE NEPHRITIS

In six patients with acute nephritis without demonstrable edema at the time of the tests with three doses of 0.1 gm. of theocin a good diuresis was produced in three, a moderate diuresis in two and no diuresis in one. If there occurred a diuresis there was an increased sodium chlorid excretion, though the amount did not increase parallel to the increase in the amount of urine. The excretion of nitrogen sometimes increased, sometimes decreased in the presence of a diuresis; more often it increased, but not as regularly as was the case with sodium chlorid, and the increase in nitrogen did not follow so closely the increase in the amount of urine as did the sodium chlorid.

Forty-eight hours following the diuretic the index of urea excretion (McLean[4]) decreased in three patients and increased in three. Of the six patients, only two had definitely abnormal indexes of urea excretion. One (Case 3) had a very low index. This was a patient who we know to have been free from nephritis several months before these observations, as he was under observation in the hospital for another condition. However, this patient, instead of improving while under observation, progressed into the picture of a subacute to chronic nephritis. The other patient with abnormal index of urea excretion had a high index, which became much higher after the diuresis.

CHRONIC NEPHRITIS

Case 1 (P. B. B. H. Med. No. 4158).—A man, aged 19, was admitted to the hospital Feb. 14, 1916, with a diagnosis of chronic nephritis. The symptoms had lasted fifteen months, following infection of diphtheria, whooping cough, measles and influenza in childhood. There was edema of the feet and legs, but

TABLE 7.—Analyses of Twenty-Four Hour Amount of Urine

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
2/21-22	978	1.017	0.34	3.33	0.36	3.52
2/22-23	834	1.018	0.38	3.17	0.39	3.25
2/23-24	810	1.016	0.52	4.21	0.31	2.51
2/24-25	718	1.016	0.39	2.8	0.24	1.72
On February 25 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
2/25-26	982	1.017	0.52	4.78	0.58	5.34
2/26-27	778	1.015	0.55	4.28	0.14	1.09
2/27-28	958	1.012	0.45	4.28	0.11	1.05

4. McLean: Jour. Exper. Med., 1915, xxii, 212, 366.

no edema at the time of the tests. The blood pressure on February 14 was systolic 130, diastolic 110; on the 18th, systolic 140, diastolic 88; on the 22d, systolic 140, diastolic 90; an on the 26th, systolic 120, diastolic 80.

A Wassermann reaction on the blood serum was negative. The urine on February 14 showed a large trace of albumin, many red blood cells, and many finely and coarsely granular, cellular, and hyaline casts. On February 26 there was a large trace of albumin and rare finely granular casts. Many fat droplets were present and an occasional red blood cell and leukocyte. The phenolsulphonephthalein excretion on February 27 was 31 per cent. in two hours. The blood urea nitrogen on February 14 was 25 mg. per 100 c.c. blood; on the 18th, 23.75 mg.; on the 24th, 13 mg., and on the 28th, 20.75 mg. The index of urea excretion (McLean) on February 14 was 16.1 per cent.; on the 18th, 21 per cent.; on the 24th, 40.1 per cent., and on the 28th, 9.5 per cent.

The diet was approximately 25 gm. of protein, 4 gm. sodium chlorid and total calories 2,000. Figure 5 illustrates graphically the daily variations as in Figure 1. Table 7 gives the urinary findings.

TABLE 8.—Analyses of Twenty-Four Hour Amount of Urine

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
2/ 8- 9	652	.....	0.55	3.59	0.22	1.43
2/ 9-10	393	.....	0.99	3.89	0.32	1.26
2/10-11	470	.....	0.8	3.76	0.31	1.46
On February 11 theocin was given, 0.3 gm. at 6 a. m. and 9 a. m.						
2/11-12	507	.....	0.57	2.89	0.5	2.54
2/12-13	405	.....	0.62	2.51	0.2	0.81
2/13-14	465	.....	0.77	3.58	0.16	0.74
2/14-15	915	.....	0.31	2.84	0.25	2.29
2/15-16	583	.....	0.82	4.78	0.19	1.11
2/16-17	1,046	.....	0.35	3.66	0.21	2.2
2/17-18	768	.....	0.6	4.61	0.26	2
2/18-19	443	.....	0.83	3.68	0.12	0.53

Case 2 (P. B. B. H. Med. No. 4109).—A woman, aged 45, was admitted to the hospital Feb. 5, 1916, with a diagnosis of chronic nephritis, hypertension, and chronic myocarditis. Her symptoms had lasted four months. She suffered with palpitation, dyspnea, and edema of the legs. There was slight edema at the time of the tests. The blood pressure on February 5 was systolic 250, diastolic 150; on the 10th, systolic 225, diastolic 145; on the 19th, systolic 200, diastolic 135; on the 23d, systolic 225, diastolic 140, and on March 2, systolic 210, diastolic 150.

A Wassermann reaction on the blood serum was negative. The urine on February 5 showed a large trace of albumin, a moderate number of finely granular and hyaline casts, and rarely a red blood cell. On the 28th there was no albumin, but many epithelial and white blood cells. The phenolsulphonephthalein excretion on February 7 was 21 per cent. in two hours, and on the 21st, 28 per cent. in two hours. The blood urea nitrogen on February 7 was 22.25 mg. per 100 c.c. blood, and on the 19th, 23 mg. per 100 c.c. blood. The

index of urea excretion (McLean) on February 7 was 26.5 per cent., and on the 19th, 20.5 per cent.

The diet from February 6 to 12 was approximately 25 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000. From February 12 to 19, approximately 75 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000.

Figure 6 illustrates graphically the daily variations, as in Figure 1. Table 8 gives the urinary findings.

Case 3 (P. B. B. H. Med. No. 4405).—A man, aged 70, was admitted to the hospital March 27, 1916, with a diagnosis of chronic nephritis, hypertension and syphilis. His symptoms had lasted two weeks. He suffered from edema of the face and legs, fulness in the abdomen, small amount of urine, and dyspnea. There was moderate edema at the time of the tests. The patient died May 4, 1916.

The Wassermann reaction of the blood serum was positive. The blood pressure on March 27 was systolic 195, diastolic 110; on April 5, systolic 160, diastolic 90; on the 17th, systolic 150, diastolic 98, and on the 29th, systolic 170, diastolic 90. The urine on March 27, showed a very large trace of albumin, with very many fine and coarsely granular casts, many leukocytes and red blood cells. On May 4 there was still a large trace of albumin, a moderate number of casts of all descriptions, and a great many red blood cells. The phenolsulphonephthalein excretion on March 28, was 17 per cent. in two hours; on the 31st, 14 per cent. in two hours, and on April 24 there was no excretion in two hours. The blood urea nitrogen on March 31, was 48.23 per cent., and on April 3, 45.67 per cent. The index of urea excretion (McLean) on March 31, was 4.35 per cent.; on April 3, 2.38 per cent.

TABLE 9.—Analyses of Twenty-Four Hour Amount of Urine

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/28/16	570	1.019	0.96	5.47	0.22	1.25
3/29/16	800	1.020	1.02	8.16	0.2	1.6
3/30/16	1,010	1.021	0.94	9.49	0.22	2.22
3/31/16	820	1.020	0.96	7.87	0.23	1.89
On April 1 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
4/ 1/16	920	1.022	1	9.2	0.23	2.12
4/ 2/16	880	1.022	1.05	9.24	0.28	1.46
4/ 3/16	930	1.019	0.99	9.12	0.37	3.4
4/ 4/16	675	1.021	1.01	6.82	0.19	1.28

The diet from March 28 to April 1, was 800 c.c. milk daily; from April 1 to April 4, approximately 25 gm. protein, 4 gm. sodium chlorid and total calories 2,000.

The urinary findings are given in Table 9.

Case 4 (P. B. B. H. Med. No. 3537).—A woman, aged 49, was admitted to the hospital Oct. 28, 1915, with a diagnosis of chronic nephritis and hypertension. The symptoms dated back two years. There were dyspnea, edema of the legs, weakness, precordial pain and palpitation. There was slight edema at the time of the tests. The blood pressure on October 28, was systolic 260, diastolic 160; on November 2, systolic 215, diastolic 140; on the 11th, systolic 220, diastolic 135, and on the 29th, systolic 220, diastolic 138.

TABLE 10.—Analyses of Two-Hour Portions of Urine

Time	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
11/12/15						
7 to 9	56	1.012	0.39	0.22	0.1	0.06
9 to 11	80	1.009	0.15	0.12	0.085	0.07
11 to 1	82	1.011	0.33	0.27	0.125	0.1
1 to 3	Lost					
3 to 5	68	1.012	0.28	0.19	0.07	0.05
5 to 7	39	1.018	0.23	0.09	0.1	0.04
7 to 9	97	1.012	0.27	0.26	0.07	0.07
9 to 7	195	1.013	0.33	0.64	0.09	0.18
Total	617	.....	....	1.79	....	0.57
11/13/15						
7 to 9	95	1.013	0.18	0.17	0.07	0.07
9 to 11	113	1.007	0.28	0.32	0.05	0.06
11 to 1	34	1.024	0.44	0.16	0.14	0.05
1 to 3	36	1.022	0.4	0.14	0.1	0.04
3 to 5	30	1.026	0.58	0.18	0.12	0.04
5 to 7	23	1.021	0.51	0.12	0.12	0.03
7 to 9	19	1.030	0.69	0.12	0.12	0.02
9 to 7	173	1.018	0.38	0.66	0.11	0.19
Total	523	.....	....	1.87	....	0.5
On Nov. 14, 1915, theocin was given, 0.5 gm. at 10 a. m. and at 6 p. m.						
11/14/15						
7 to 9	58	1.012	0.08	0.05	0.08	0.05
9 to 11	350	1.008	0.04	0.14	0.15	0.53
11 to 1	258	1.006	0.06	0.16	0.3	0.77
1 to 3	177	1.006	0.11	0.19	0.25	0.44
3 to 5	290	1.008	0.07	0.2	0.2	0.58
5 to 7	125	1.010	0.07	0.1	0.21	0.28
7 to 9	59	1.012	0.1	0.06	0.24	0.14
9 to 7	130	1.019	0.34	0.44	0.22	0.3
Total	457	.....	....	1.34	....	3.09
11/15/15						
7 to 9	33	1.016	0.64	0.21	0.16	0.05
9 to 11	42	1.016	0.46	0.19	0.12	0.05
11 to 1 1 to 3	44	1.022	0.54	0.24	0.17	0.08
3 to 5	34	1.022	0.46	0.16	0.19	0.07
5 to 7	41	1.016	0.34	0.14	0.1	0.04
7 to 9	50	1.015	0.43	0.22	0.07	0.04
9 to 7	163	1.012	0.25	0.41	0.06	0.09
Total	407	.....	....	1.57	....	0.42

TABLE 11.—Analyses of Two-Hour Portions of Urine

Time	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
11/1/15						
7 to 9	75	1.019	6.7	0.51	0.25	0.19
9 to 11	91	1.016	5.4	0.49	0.25	0.23
11 to 1	190	1.012	2.1	0.4	0.14	0.27
1 to 3	200	1.013	2.6	0.52	0.14	0.28
3 to 5	120	1.018	5	0.62	0.19	0.23
5 to 7	100	1.015	4.2	0.42	0.16	0.16
7 to 9	210	1.013	4	0.84	0.17	0.36
9 to 7	740	1.012	4	2.96	0.13	0.96
Total	1,726	.....	....	6.76	....	2.68
11/2/15						
7 to 9	26	1.024	5	0.13	0.26	0.07
9 to 11	135	1.016	5.4	0.73	0.26	0.35
11 to 1	185	1.013	2.9	0.54	0.11	0.2
1 to 3	235	1.011	2.7	0.64	0.1	0.24
3 to 5	215	1.010	3.1	0.67	0.13	0.28
5 to 7	330	1.011	1.7	0.56	0.09	0.3
7 to 9	268	1.011	2.6	0.6	0.11	0.3
9 to 7	550	1.012	3.6	1.98	0.12	0.66
Total	1,944	.....	....	5.85	....	2.4
On Nov. 3, 1915, theocin was given, 0.5 gm. at 10 a. m. and 2 p. m.						
11/3/15						
7 to 9	97	1.016	4.1	0.4	0.22	0.21
9 to 11	390	1.010	1.6	0.62	0.18	0.7
11 to 1	450	1.010	1.4	0.63	0.255	0.35
1 to 3	330	1.010	1.8	0.59	0.215	0.71
3 to 5	240	1.011	2.4	0.68	0.21	0.5
5 to 7	155	1.012	1.3	0.2	0.16	0.25
7 to 9	155	1.012	2.8	0.43	0.18	0.28
9 to 7	450	1.013	2.8	1.26	0.12	0.54
Total	2,267	.....	....	4.81	....	3.54
11/4/15						
7 to 9	85	1.019	3.7	0.33	0.2	0.17
9 to 11	110	1.013	4	0.44	0.21	0.23
11 to 1	115	1.015	2.4	0.28	0.18	0.21
1 to 3	220	1.011	1.9	0.43	0.12	0.26
3 to 5	150	1.011	3	0.45	0.12	0.18
5 to 7	155	1.012	2.8	0.43	0.1	0.16
7 to 9	155	1.013	2.4	0.37	0.11	0.17
9 to 7	455	1.014	4.1	1.88	0.1	0.46
Total	1,445	.....	....	4.51	....	1.84

The Wassermann reaction on the blood serum was negative. The urine on October 29, showed a slight trace of albumin, a few epithelial cells, no casts and no red blood cells. On December 1, there was no trace of albumin, but many finely granular and hyaline casts, many epithelial cells and a few leukocytes. The phenolsulphonephthalein excretion on November 1, was 52.5 per cent. in two hours; on December 2, 60 per cent. in two hours. The blood urea nitrogen on November 1, was 8.37 mg. per 100 c.c. blood; on the 13th, 10.50 mg., and on the 15th, 16.87 mg. The index of urea excretion (McLean) on November 1, was 120 per cent.; on the 13th, 58.5 per cent., and on the 15th, 23.5 per cent.

The diet was approximately 25 gm. protein, 4 gm. sodium chlorid and total calories 2,000. Figures 7, 8 and 9 illustrate graphically two-hour variations during the day in the amount of urine and in the total nitrogen and sodium chlorid, as well as in its specific gravity and the percentage concentration of sodium chlorid and nitrogen. In addition these same factors are shown in the night portion and the proportionate amount of night to day urine. There also appears the twenty-four hour amount of urine in relation to the twenty-four hour intake of fluid in several days preceding the test day. Figure 8 illustrates these same factors as influenced by two doses of 0.5 gm. each of theocin. Table 10 gives the urinary findings.

Case 5 (P. B. B. H. Med. No. 3369).—A man, aged 32, was admitted to the hospital Sept. 25, 1915, with a diagnosis of chronic nephritis and hypertension, from which he had suffered four months. He showed symptoms of general edema, dyspnea and failing eyesight. There was very slight edema at the time of the tests. The blood pressure on September 25, was systolic 205, diastolic 135; on October 6, systolic 192, diastolic 135; on October 26, systolic 190, diastolic 120, and on November 10, systolic 210, diastolic 112.

The Wassermann reaction of the blood serum was negative. The urine on September 25, showed a large amount of albumin and many coarsely granular casts, a few hyaline casts containing fat droplets, and many leukocytes. On November 10 there was still a large amount of albumin, numerous hyaline, granular and cellular casts, and numerous leukocytes, with an occasional red blood cell. The phenolsulphonephthalein excretion on September 26 was 36 per cent. in two hours; on October 8, 43 per cent. in two hours, and on October 19, 44 per cent. in two hours. The blood urea nitrogen on September 28 was 23 mg. per 100 c.c. blood; on October 7, 18.12 mg.; on November 2, 29.75 mg., and on November 4, 20 mg. The index of urea excretion (McLean) on September 28 was 21.5 per cent.; on October 7, 45.5 per cent.; on November 2, 20.4 per cent., and on November 4, 16.1 per cent.

The diet was approximately 75 gm. of protein, 4 gm. sodium chlorid, total calories 2,800.

Figures 10, 11 and 12 illustrate graphically two-hour variations during the day in the amount of urine and in the total nitrogen and sodium chlorid, as well as in its specific gravity and the percentage concentration of sodium chlorid and nitrogen. In addition, these same factors are shown in the night portion and the proportionate amount of night to day urine. There also appears the twenty-four hour amount of urine in relation to the twenty-four hour intake of fluid in several days preceding the test day. Figure 11 illustrates these same factors as influenced by two doses of 0.5 gm. each of theocin. Table 11 gives the urinary findings.

SUMMARY OF CASES OF CHRONIC NEPHRITIS

In five patients with chronic nephritis, all except one of whom had some edema at the time of the tests, theocin in varying doses (totals of 0.3 gm., 0.9 gm. and 1 gm.) produced a moderate diuresis in one, a slight diuresis in three and no diuresis in one. In all there was an

increased excretion of sodium chlorid, even in the patient who had no diuresis. The amount of nitrogen excreted was increased in two patients and decreased in three. The index of urea excretion was decreased in three patients, increased in one, while in the fifth the determination was not made close enough to the diuresis to be of any significance. In all of these the index of urea excretion was below normal. In the two patients in which the two hour renal test was carried on during the several days of the testing (Cases 4 and 5, Figs. 7, 8, 9, 10, 11, and 12) this form of test shows a decreased power of concentration during the day on which theocin was given with an almost complete return on the day following to the condition existing prior to giving the theocin.

CHRONIC CARDIORENAL DISEASE

CASE 1 (P. B. B. H. Med. No. 3737).—A man, aged 61, was admitted to the hospital Dec. 6, 1915, with a diagnosis of chronic myocarditis, chronic nephritis, and terminal lobar pneumonia. The symptoms had lasted two years. There were dyspnea, edema, and tenderness over the liver. There was marked edema at the time of the tests. The blood pressure on December 7 was systolic 165, diastolic 125; on the 14th, systolic 160, diastolic 105, and on the 22d, systolic 145, diastolic 110.

The Wassermann reaction on the blood serum was negative. The phenolsulphonephthalein excretion on December 14 was 30 per cent. in two hours. The blood urea nitrogen on December 7 was 22.75 mg. per 100 c.c. blood. The index of urea excretion (McLean) on December 7 was 19.95 per cent.

TABLE 12.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
4/19/16	880	1.029	1.65	8.58	0.19	0.99
4/20/16	465	1.029	1.74	8.09	0.28	1.3
4/21/16	695	1.025	1.75	12.16	0.48	3.34
On April 22 theocin was given, 0.2 gm. at 6 a. m., 9 a. m. and 12 noon.						
4/22/16	1,980	1.017	0.71	14.06	0.98	19.4
4/23/16	1,200	1.018	0.8	9.6	0.95	11.4
4/24/16	540	1.019	1.31	7.07	0.54	2.92
4/25/16	360	1.020	1.28	4.61	0.13	0.47
4/26/16	300	1.029	1.80	5.67	0.04	0.12

Figure 13 shows the amount of diuresis produced by three doses of 0.5 gm. each of theocin with and without an accompanying digitalis treatment.

CASE 2 (P. B. B. H. Med. No. 4529).—A man, aged 66, was admitted to the hospital April 18, 1916, with a diagnosis of chronic myocarditis and auricular fibrillation. The symptoms had lasted thirteen months. There were dyspnea and edema of the legs. There was marked edema at the time of the tests. The patient died May 17, 1916. The blood pressure on April 18 was

systolic 125, diastolic 85; on the 26th, systolic 140, diastolic 100; on the 29th, systolic 130, diastolic 90, and on May 5, systolic 120, diastolic 100.

The Wassermann reaction on the blood serum was negative. The urine on April 18 showed a slight trace of albumin and a moderate number of hyaline and finely granular casts. On May 4 there was the slightest possible trace of albumin and a moderate number of hyaline and finely granular casts. The phenolsulphonephthalein excretion on April 18 was 17 per cent. in two hours; on the 25th, 19 per cent. in two hours. The blood urea nitrogen on April 21 was 35.64 mg. per 100 c.c. blood, and on the 24th, 21.67 mg. The index of urea excretion (McLean) on April 21 was 72.6 per cent., and on the 24th 88.5 per cent.

The diet was 800 c.c. milk daily.

Figure 14 illustrates graphically the daily variation as in Figure 1. Table 12 gives the urinary findings.

TABLE 13.—Analyses of Twenty-Four Hour Amount of Urine

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
4/16/16	840	1.023	0.98	8.23	0.98	8.23
4/17/16	845	1.024	1.19	10.06	0.94	7.94
4/18/16	606	1.024	1.13	6.85	0.91	5.52
On April 19 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and at 6 p. m.						
4/19/16	1,153	1.021	0.82	9.46	1.1	12.68
4/20/16	650	1.025	0.88	5.72	1.09	7.09
4/21/16	870	1.023	1.06	9.22	1.05	9.14
4/22/16	730	1.023	1.04	7.59	1	7.3
4/23/16	1,215	1.023	1.19	14.46	0.94	11.42
On April 24 theocin was given, 0.2 gm. at 6 a. m. and at 10 a. m.						
4/24/16	1,580	1.018	0.64	9.73	1.12	17.02
4/25/16	1,700	1.014	0.59	10.03	0.84	14.28
4/26/16	1,851	1.014	0.57	7.13	0.48	6.01
4/27/16	1,562	1.013	0.58	9.06	0.46	7.19
4/28/16	635	1.020	0.95	6.03	0.45	2.86

Case 3 (P. B. B. H. Med. No. 4414).—A man, aged 41, was admitted to the hospital March 28, 1916, with a diagnosis of syphilitic aortitis, dilatation of arch of aorta, aortic insufficiency and chronic nephritis. The symptoms had lasted three years. The patient complained of dyspnea and edema of legs. There was edema at the time of the tests. The blood pressure on April 13 was systolic 138, diastolic 50.

The Wassermann reaction on the blood serum was positive. The urine on April 28 showed the slightest possible trace of albumin and a few hyaline and granular casts, and on the 30th the slightest possible trace of albumin and an occasional hyaline cast. The phenolsulphonephthalein excretion on April 18 was 37 per cent.; on the 21st, 38 per cent., and on the 26th, 34 per cent. The blood urea nitrogen on April 18 was 25.86 mg. per 100 c.c. blood; on the 21st, 21.90 mg., and on the 26th, 18.40 mg. The index of urea excretion

TABLE 14.—Analyses of Two-Hour Portions of Urine

Time	C.c. Volume,	Sp. Gr.	Nitrogen Per Cent.	Nitrogen Grams	Chlorid Per Cent.	Chlorid Grams
12/13/15						
7 to 9	.....	.....	....	....	....	....
9 to 11	42	.....	1.44	0.61	0.4	0.17
11 to 1	38	1.024	0.9	0.34	0.4	0.15
1 to 3	31	1.026	0.66	0.21	0.38	0 11
3 to 5	66	1.027	1.09	0.72	0.63	0.42
5 to 7	51	1.025	1.1	0.56	0.66	0.34
7 to 9	38	1.026	1.08	0.41	0.72	0.27
9 to 7	129	1.028	1.34	1.86	0.4	0.56
Total	405	.....	....	4.71	....	2.02
12/14/15						
7 to 9	42	1.022	1.36	0.57	0.36	0.15
9 to 11	16	1.022	0.92	0.15	0.4	0.06
11 to 1	43	1.026	0.62	0.27	0.4	0.17
1 to 3	44	1.028	0.96	0.42	0.42	0.19
3 to 5	47	1.024	0.97	0.46	0.55	0.26
5 to 7 / 7 to 9	85	1.026	1.44	1.22	0.43	0.36
9 to 7	12	1.030	0.42	0.05	0.4	0.05
Total	289	.....	....	3.14	....	1.34
12/15/15						
7 to 9	162	1.022	1.17	1.91	0.44	0.72
9 to 11	66	1.022	1.01	0.67	0.56	0.37
11 to 1	34	1.028	1.1	0.37	0.78	0.27
1 to 3	54	1.023	0.95	0.51	0.76	0.41
3 to 5	71	1.021	0.72	0.51	0.85	0.6
5 to 7	36	1.029	1.04	0.37	0.74	0.27
7 to 9 / 9 to 7	282	1.022	0.61	1.4	0.92	2.59
Total	706	.....	....	5.74	....	5.23
On Dec. 16, 1915, theocin was given, 0.3 gm. at 6 a. m., 9 a. m. and 12 noon.						
12/16/15						
7 to 9	448	1.012	0.1	0.45	0.56	2.85
9 to 11	620	1.009	0.08	0.5	0.39	2.66
11 to 1	810	1.009	0.04	0.32	0.52	4.21
1 to 3	550	1.008	0.08	0.32	0.47	2.59
3 to 5	630	1.006	0.06	0.39	0.4	2.52
5 to 7	270	1.010	0.07	0.19	0.39	1.05
7 to 9	230	1.010	0.1	0.23	0.33	0.76
9 to 7	590	1.014	0.16	0.94	0.41	2.42
Total	4,148	.....	....	3.35	....	21.06

TABLE 14.—Analyses of Two-Hour Portions of Urine—(*Continued*)

Time	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
12/17/15						
7 to 9	32	1.017	0.3	0.16	0.32	0.17
9 to 11	7	.....	0.41	0.03	0.2	0.01
11 to 1	120	1.022	0.43	0.52	0.29	0.35
1 to 3						
3 to 5	53	1.023	1.04	0.55	0.32	0.17
5 to 7	36	1.022	0.86	0.33	0.3	0.11
7 to 9	55	1.024	0.39	0.22	0.25	0.14
9 to 7	80	1.024	0.48	0.43	0.27	0.24
Total	414	.....	....	2.24	....	1.19

(McLean) on April 18 was 48.2 per cent.; on the 21st, 36.3 per cent., and on the 26th, 35.2 per cent.

The diet from April 14 to 24 was the general house diet. From April 25 to 28 it was approximately 75 gm. protein, 4 gm. sodium chlorid and total calories 2,000. Table 13 gives the urinary findings.

Case 4 (P. B. B. H. Med. No. 3777).—A man, aged 20, was admitted to the hospital Dec. 11, 1915, with a diagnosis of chronic pericarditis, ascites, and possibly adherent pericardium, the symptoms of which had lasted two months. He complained of dyspnea, edema of the legs and abdomen, with ascites. There was marked edema at the time of the tests. The blood pressure on December 11 was systolic 100, diastolic not obtained; on the 14th, systolic 128, diastolic 116, and on January 13, systolic 118, diastolic 100.

The Wassermann reaction on the blood serum was negative. The urine on December 11 showed slight trace of albumin with frequent hyaline and granular casts and rare red blood cells; on January 16 there was the slightest possible trace of albumin with a few leukocytes, no red blood cells and no casts. The phenolsulphonephthalein excretion on December 21 was 50 per cent. in two hours. The blood urea nitrogen on December 13 was 12.12 mg. per 100 c.c. of blood; on the 17th, 9.12 mg.; and on January 8, 12.50 mg. The index of urea excretion on December 13 was 257.5 per cent.; on the 17th, 22.7 per cent., and on January 8, 176 per cent.

The diet was soft solids.

Figures 15, 16 and 17 illustrate graphically the two-hour variations during the day in the amount of urine and in the total nitrogen and sodium chlorid, as well as in its specific gravity and the percentage concentration of sodium chlorid and nitrogen. In addition these same factors are shown in the night portion and the proportionate amount of night to day urine. There also appears the twenty-four hour amount of urine in relation to the twenty-four hour intake of fluid in several days preceding the test day. Figure 16 illustrates these same factors as influenced by three doses of theocin of 0.3 gm. each. Table 14 gives the urinary findings.

Case 5 (P. B. B. H. Med. No. 3337).—A man, aged 27, was admitted to the hospital Sept. 14, 1915, with a diagnosis of chronic cardiac valvular disease with mitral stenosis and insufficiency and chronic myocarditis and syphilis, the symptoms having lasted thirteen months. The patient complained of

TABLE 15.—Analyses of Two-Hour Portions of Urine

Time	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
11/14/15 7 to 9	64	1.026	0.96	0.61	1.05	0.67
9 to 11	92	1.020	0.21	0.19	0.64	0.59
11 to 1	250	1.008	0.12	0.3	0.17	0.43
1 to 3	285	1.010	0.26	0.74	0.17	0.49
3 to 7	175	1.019	0.64	1.12	0.33	0.58
7 to 9	70	1.026	0.94	0.66	0.37	0.26
9 to 7	200	1.026	1.46	2.92	0.37	0.74
Total	1,136	.....	....	6.54	....	3.76
11/15/15 7 to 9	85	1.023	0.7	0.6	0.67	0.57
9 to 11	81	1.017	0.55	0.45	0.55	0.45
11 to 1	225	1.015	0.34	0.77	0.56	1.16
1 to 3	465	1.012	0.18	0.84	0.24	1.12
3 to 5	152	1.013	0.44	0.67	0.37	0.56
5 to 7	69	1.022	0.78	0.54	0.54	0.37
7 to 9	332	1.011	0.27	0.9	0.14	0.47
9 to 7	340	1.015	0.45	1.53	0.25	0.85
Total	1,749	.....	....	6.3	....	5.55
On Nov. 16, 1915, theocin was given, 0.5 gm. at 10 a. m. and 2 p. m.						
11/16/15 7 to 9	85	1.016	0.54	0.46	0.4	0.34
9 to 11	48	1.027	0.83	0.4	0.845	0.41
11 to 1	83	1.025	0.75	0.61	0.98	0.81
1 to 3	183	1.017	0.57	1.04	0.47	0.86
3 to 5	330	1.010	0.28	0.92	0.44	1.45
5 to 7	485	1.010	0.07	0.32	0.25	1.21
7 to 9	248	1.015	0.3	0.74	0.4	0.99
9 to 7	248	1.023	0.76	1.69	0.2	0.5
Total	1,710	.....	....	6.18	....	6.57
11/17/15 7 to 11	680	1.007	0.06	0.41	0.03	0.2
11 to 1	289	1.009	0.28	0.81	0.07	0.19
1 to 3	245	1.010	0.31	0.76	0.11	0.27
3 to 5	262	1.009	0.27	0.71	0.1	0.26
5 to 7	69	1.021	1.11	0.77	0.155	0.11
7 to 9	60	1.022	0.81	0.49	0.22	0.13
9 to 7	178	1.024	1.44	2.56	0.13	0.23
Total	1,783	.....	....	6.51	....	1.39

TABLE 16.—Analyses of Two-Hour Portions of Urine

Time	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
11/29/15						
7 to 9	95	1.025	0.48	0.46	0.96	0.91
9 to 11	125	1.022	0.64	0.8	0.88	1.1
11 to 1	82	1.022	1	0.82	0.85	0.7
1 to 3	178	1.011	0.17	0.3	0.45	0.8
3 to 5	98	1.022	0.67	0.66	0.74	0.73
5 to 7	55	1.021	0.62	0.34	0.66	0.36
7 to 9	230	1.012	0.34	0.78	0.33	0.76
9 to 7	420	1.019	0.26	0.51	0.51	2.14
Total	1,283	.....	....	4.67	....	7.5
11/30/15						
7 to 9	208	1.013	0.19	0.4	0.42	0.87
9 to 11	485	1.009	0.24	1.1	0.3	1.37
11 to 1	114	1.015	0.52	0.59	0.5	0.57
1 to 3	484	1.010	0.12	0.58	0.17	0.82
3 to 5	227	1.012	0.5	0.68	0.33	0.97
5 to 7 7 to 9	117	1.017	0.55	0.64	0.36	0.42
9 to 7	249	1.020	0.86	2.14	0.41	1.02
Total	1,857	.....	....	6.13	....	6.04
On Dec. 1, 1915, theocin was given, 0.5 gm. at 10 a. m. and 2 p. m.						
12/1/15						
7 to 9	98	1.019	0.67	0.67	0.57	0.56
9 to 11	258	1.012	0.2	0.52	0.25	0.65
11 to 1	220	1.013	0.37	0.68	0.51	1.12
1 to 2:30	204	1.012	0.17	0.35	0.39	0.8
2:30 to 5	197	1.013	0.38	0.75	0.45	0.87
5 to 7	204	1.015	0.54	1.1	0.41	0.84
7 to 9	133	1.017	0.4	0.53	0.36	0.48
9 to 7	218	1.020	0.75	1.64	0.33	0.72
Total	1,532	.....	....	6.24	....	6.04
12/2/15						
7 to 9	91	1.026	0.22	0.2	0.44	0.4
9 to 11:18	67	1.026	1.27	0.83	0.39	0.26
11:18 to 1	38	1.032	0.82	0.31	0.4	0.15
1 to 3	70	1.026	1.2	0.84	0.33	0.23
3 to 5	69	1.028	0.87	0.6	0.31	0.21
5 to 7	65	1.028	1.37	0.89	0.22	0.14
7 to 9	59	1.028	1.31	0.81	0.17	0.1
9 to 7	90	1.029	1.42	1.28	0.16	0.14
Total	549	.....	....	5.76	....	1.63

dizziness and dyspnea. There was edema at the time of the tests. The patient died Jan. 2, 1916. The blood pressure on September 14 was systolic 105, diastolic 75; on the 24th, systolic 110, diastolic 90.

The Wassermann reaction on the blood serum was positive. The urine on September 14 showed a slight trace of albumin, with frequent hyaline and granular casts. On November 19 there was a slight trace of albumin, but no casts and but few leukocytes. The phenolsulphonephthalein excretion on September 21 was 63 per cent. in two hours. The blood urea nitrogen on November 15 was 20.62 mg. per 100 c.c. of blood, and on the 17th, 35 mg. The index of urea excretion on November 15 was 102 per cent., and on the 17th, 68 per cent.

The diet was approximately 75 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000. Table 15 gives the urinary findings.

Case 6 (P. B. B. H. Med. No. 3602).—A man, aged 64, was admitted to the hospital Nov. 11, 1915, with a diagnosis of hypertension, arteriosclerosis and cerebral hemorrhage. It had been twenty-four hours since the onset of the hemiplegia. There was dizziness, hemiplegia, but no edema at the time of the tests. The blood prssure on November 12 was systolic 182, diastolic 98; on the 19th, systolic 150, diastolic 80; on the 29th, systolic 165, diastolic 95, and on December 8, systolic 155, diastolic 85.

The Wassermann reaction of the blood serum was negative. The urine on November 11 showed no albumin and no casts. The same condition existed on December 7. The phenolsulphonephthalein excretion on November 11 was 84 per cent. in two hours, and on the 18th, 65 per cent. in two hours. The blood urea nitrogen on November 19 was 30 mg. per 100 c.c. blood; on the 30th, 12.75 mg., and on December 2, 12.25 mg. The index of urea excretion on November 19 was 635 per cent; on the 30th, 132.5 per cent., and on December 2, 180 per cent.

The diet was approximately 75 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000. The urinary findings are given in Table 16.

SUMMARY OF CASES OF CHRONIC CARDIORENAL DISEASES

In six patients with chronic cardiorenal disease theocin in varying doses (totals of 0.3 gm., 0.6 gm., 0.9 gm., 1 gm. and 1.5 gm.) produced a marked diuresis in four and no diuresis in two. In the patients who had no diuresis there was no edema present at the time of the tests and during that period there were no signs of cardiac decompensation. In one of the four patients with marked diuresis no quantitations of nitrogen and sodium chlorid were made. In the other three there was a markedly increased excretion of sodium chlorid, while in two the nitrogen excretion was slightly increased, and in one it was decreased. In the two patients without diuresis sodium chlorid excretion was slightly increased in one, slightly decreased in the other, while nitrogen excretion was unchanged in one and slightly decreased in the other. In the three patients with marked diuresis in which the index of urea excretion was determined, one showed a slight increase, one a slight decrease and one a strikingly large decrease. In the two patients with no diuresis one showed an increased and one a decreased index. One patient in this series had a high index of urea excretion and one an index moderately, though definitely below normal. In the others the

indexes were within normal limits. In the three patients (Case 4, Figures 15, 16 and 17, and Cases 5 and 6) in whom the two-hour renal test was carried out on the several days before and after giving theocin, this test showed very little difference in the figures on days preceding and following the theocin.

COMMENT

In this series of patients it is seen that theocin has no constant diuretic action. In patients with little or no demonstrable edema theocin may produce a moderate degree of diuresis (expressed roughly as good in three patients, moderate in three and slight in three) or it may produce no diuresis (four patients). In none of our cases of pure nephritis was there any very great amount of edema at the time the tests were made. In four cardiorenal cases, however, there was a very considerable degree of edema and in these a much greater diuresis was produced by theocin. When a diuresis occurred almost always sodium chlorid excretion was increased, but the increase was not parallel to the increase in fluid, though usually the increase in excretion was most marked in those patients in whom occurred the greatest increase in urine output. Sometimes with rather small increases in urine output, sodium chlorid excretion was considerably increased. In contrast to sodium chlorid, nitrogen excretion was increased less frequently and usually to a less degree. In half of the cases studied nitrogen excretion decreased after giving theocin. Even in patients with a marked diuresis nitrogen excretion might be but little increased or even decreased.

If we consider the question of the therapeutic efficiency of theocin as a diuretic in the light of the above results we would be justified to express skepticism of its value in patients with relatively little demonstrable edema. In the first place an increased urine output is not constant after theocin, though it often occurs. If we give a diuretic to a patient with acute or chronic nephritis having only moderate edema, what might be considered to be the therapeutic effect we are seeking? In such a case the edema in itself is rarely doing much harm. So to remove a large amount of fluid, even were that the result from giving the diuretic, would not in itself be of much therapeutic value. Very likely the patient is toxic and shows signs of uremia. In such an event we might seek by a diuretic to increase elimination through the kidney. Theocin in these cases of ours caused usually an increased elimination of sodium chlorid and water, but we have no evidence that sodium chlorid retention is harmful unless it is a factor in the production of a disturbing edema. There is more evidence that nitrogenous substances of some kind are toxic, but, as we have seen, nitrogen elimination is

much less constantly increased by theocin and quite often is actually decreased. So, from this point of view we might question the therapeutic efficiency of theocin in cases of nephritis with moderate amounts of edema. Perhaps we can assume that the reason for using a diuretic in this type of case is to increase renal efficiency, to stimulate the kidney to increased work. Measured by water or sodium chlorid output, theocin might be said to accomplish this; measured by nitrogen elimination, function is little improved, often is made worse. Renal efficiency, as measured by the index of urea excretion in cases of acute or chronic nephritis, we have found in our cases to be more often decreased than increased after using theocin, so that the evidence here is against rather than in favor of an increase in renal efficiency from the use of theocin.

Now if we turn to cases in which there is a large element of cardiac insufficiency, we have found that theocin very commonly, especially when used in combination with digitalis, causes an active diuresis, especially in patients with marked edema. In them salt output usually is markedly increased. On the other hand, nitrogen excretion often is but little increased, sometimes actually decreased. In these patients edema is a troublesome symptom. To remove it helps the patient. Theocin is effective in producing a large diuresis and so decreases edema and in this sense is therapeutically efficient. These patients, as a rule, are not toxic and removal of nitrogenous substances is not what is sought from theocin. Even in cases of this group a marked diuresis from theocin is often followed by a drop in the index of urea excretion, suggesting that following great renal activity comes a period of depressed renal function. If this is true, then an intermittent dosage with theocin with interveining periods in which no diuretic is given is probably the best procedure to follow with cases of the cardiorenal group having considerable or marked edema. In a very considerable number of patients with cardiorenal disease we have found theocin to be effective in this sense, used in this way, so that our observations here reported on a few patients with cardiorenal edema in which sodium chlorid and nitrogen elimination and the index of urea excretion were studied are in accord, so far as the effectiveness of theocin in producing diuresis is concerned, with our observations on a number of patients in whom these detailed studies were not made.

The study here reported is of relatively few cases and of but one diuretic (theocin). This being the case, it must be realized that far-reaching conclusions are unjustified. Those that have been drawn should be regarded as merely suggestive. They are, however, quite in

accord with the view previously expressed by myself with regard to diuretics, views based on animal experimentation and various methods of clinical observation.

SUMMARY

A fairly complete study of a small group of patients with acute nephritis or chronic nephritis or cardiorenal disease indicates that theocin in patients with slight or no edema has little or no therapeutic value, inasmuch as diuresis is not constantly produced, elimination of nitrogenous substances quite often is slightly if at all increased and renal function is frequently decreased after giving theocin. In cardiorenal cases with marked edema theocin is of therapeutic value, because it produces, especially in conjunction with digitalis, an active diuresis with increased sodium chlorid elimination, which decreases edema, a troublesome feature in these cases. Inasmuch as there is evidence that following an active diuresis renal function is depressed, an intermittent usage of theocin seems preferable to a continuous usage in cardiorenal cases with edema.

Peter Bent Brigham Hospital.

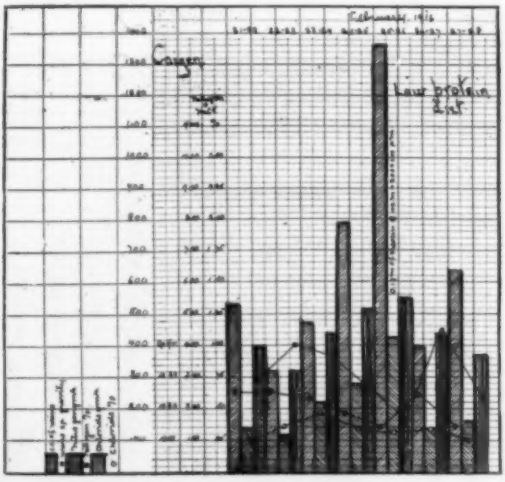

Fig. 1.—Acute nephritis, Case 1. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On February 25 the patient received three doses of 0.1 gm. each of theocin.

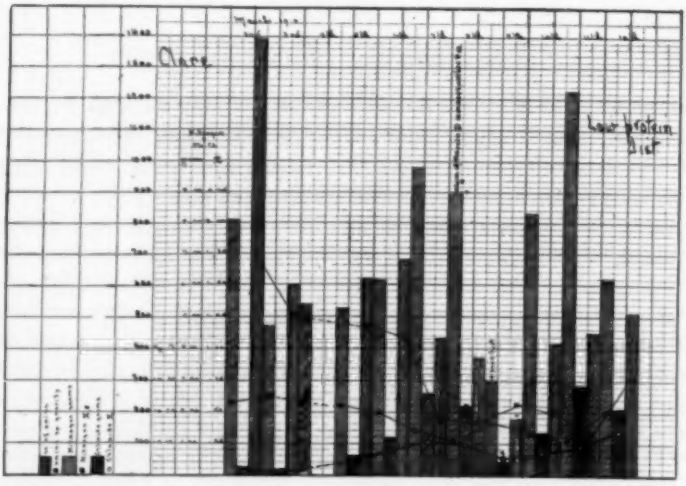

Fig. 2.—Acute nephritis, Case 2. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On March 8 the patient received three doses of 0.1 gm. each of theocin.

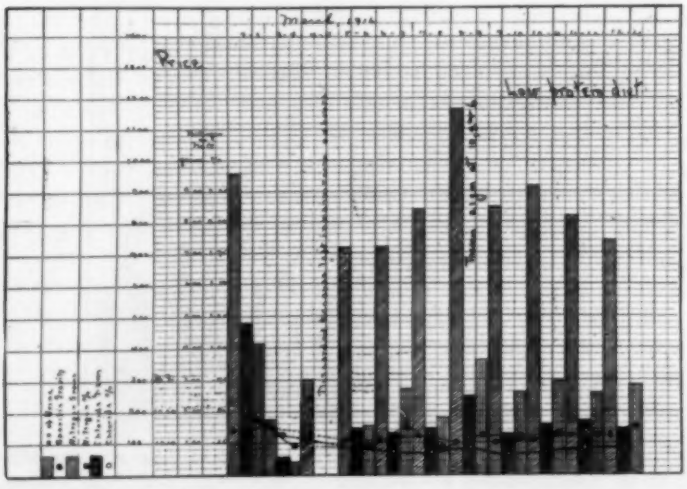

Fig. 3.—Acute nephritis, Case 3. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On March 8 the patient received three doses of 0.1 gm. each of theocin.

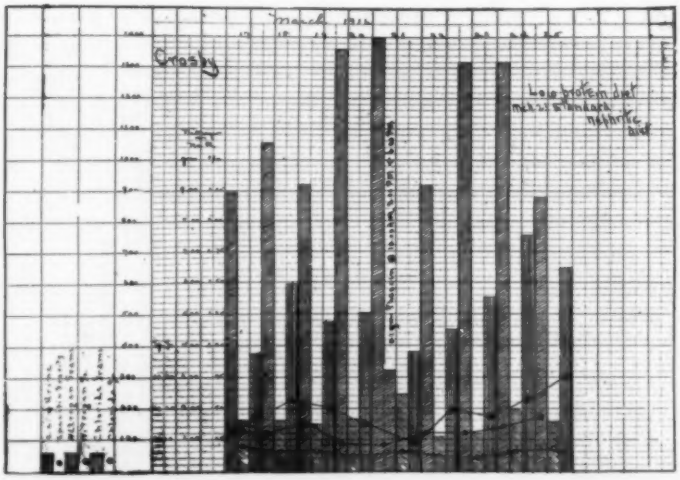

Fig. 4.—Acute nephritis, Case 4. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On March 21 the patient received three doses of 0.1 gm. each of theocin.

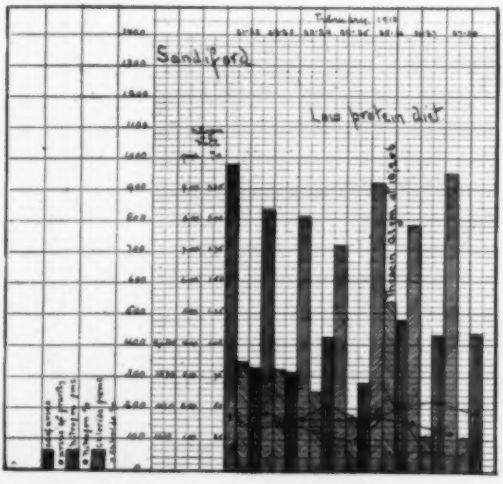

Fig. 5.—Chronic nephritis, Case 1.—The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On February 25 the patient received three doses of 0.1 gm. each of theocin.

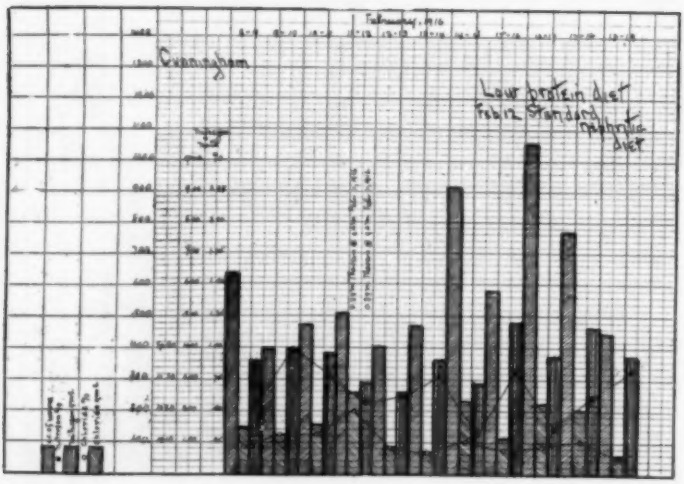

Fig. 6.—Chronic nephritis, Case 2. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On February 11 the patient received two doses of 0.3 gm. each of theocin.

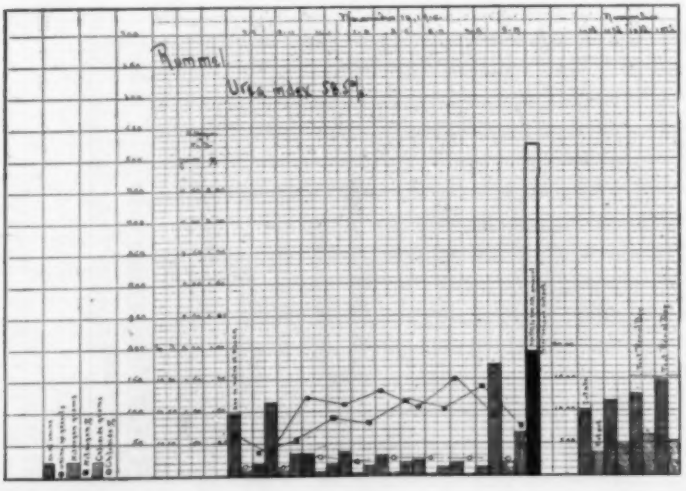

Fig. 7.—Chronic nephritis, Case 4, test of November 13. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

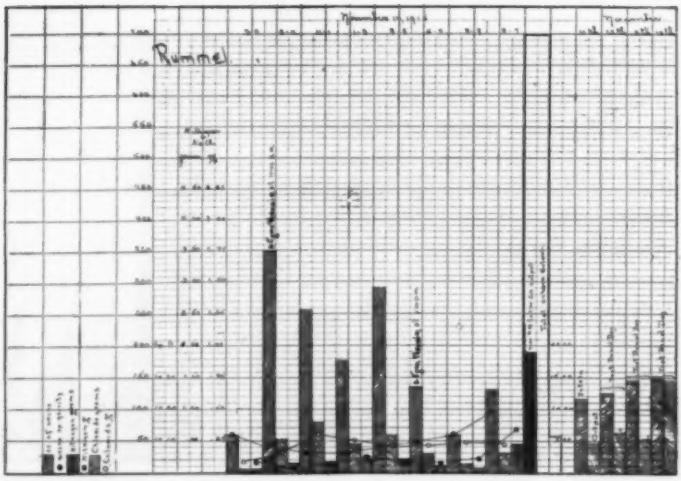

Fig. 8.—Same case as shown in Figure 7, test of November 14. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

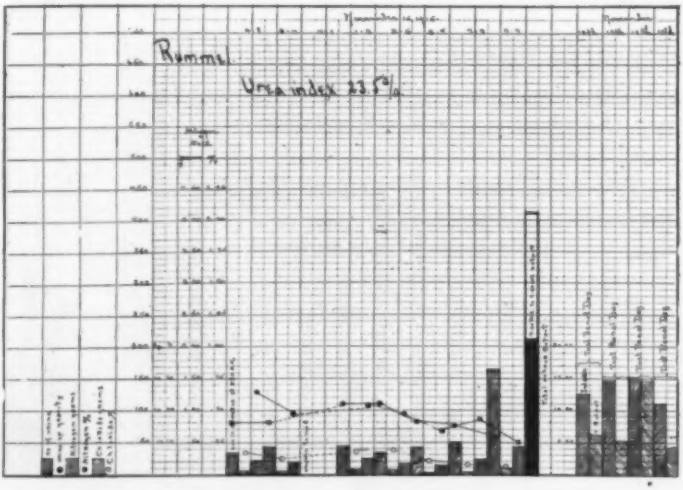

Fig. 9.—Same case as shown in Figure 7 and 8, test of November 15. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

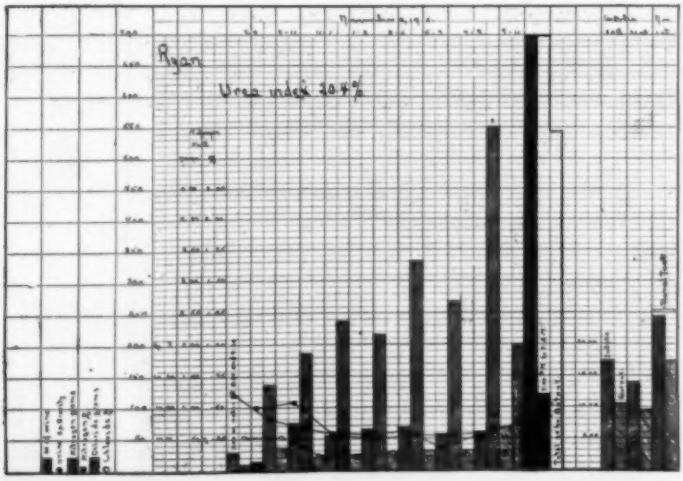

Fig. 10.—Chronic nephritis, Case 5, test on November 2. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

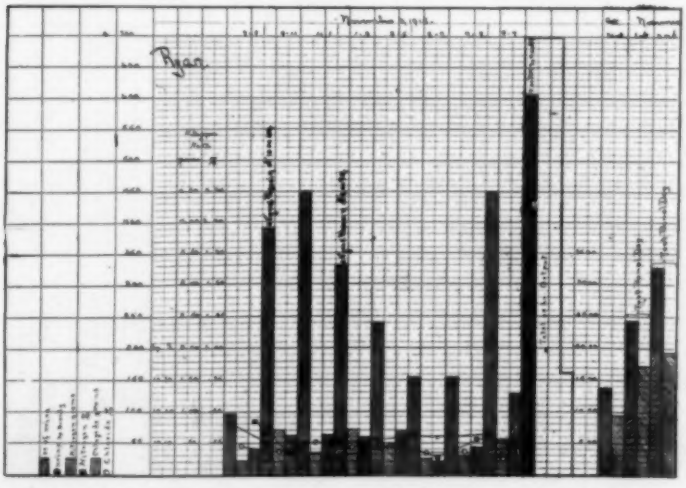

Fig. 11.—Same case as shown in Figure 10, test on November 3. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

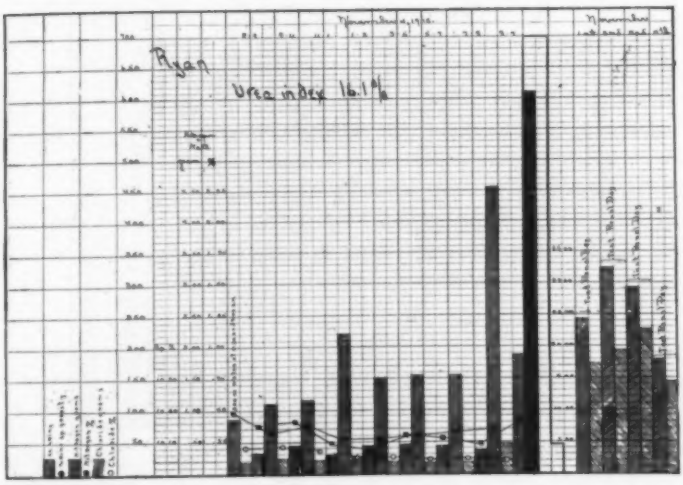

Fig. 12.—Same case as shown in Figures 10 and 11, test on November 4. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and the urine output in the days preceding the test day.

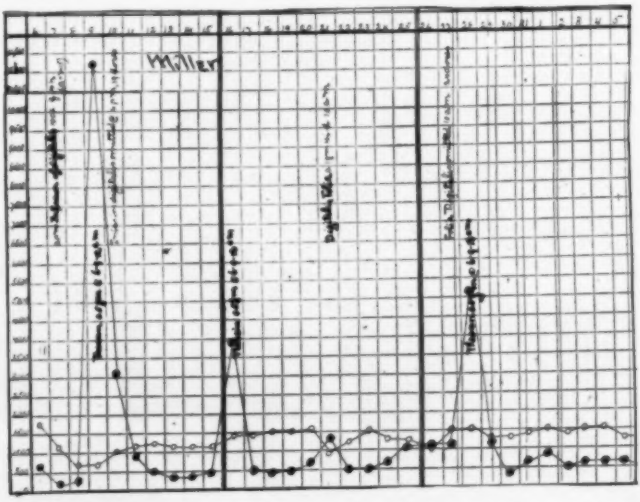

Fig. 13.—Cardiorenal disease, Case 1. The black dots and connecting lines indicate the amount of urine in cubic centimeters. The circles connected by lines indicate the fluid intake of the patient in cubic centimeters.

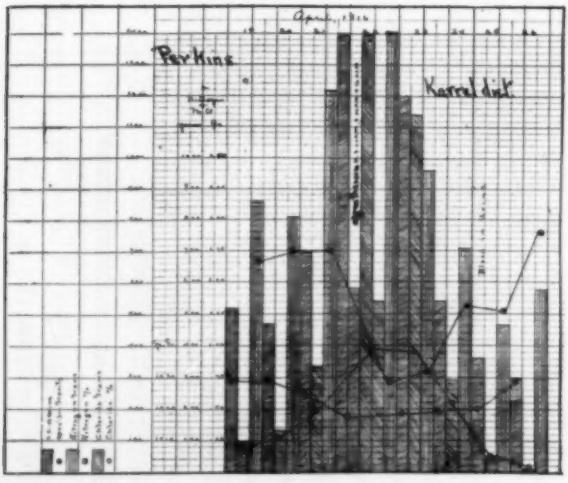

Fig. 14.—Cardiorenal disease, Case 2. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On April 22 the patient received three doses of 0.2 gm. each of theocin.

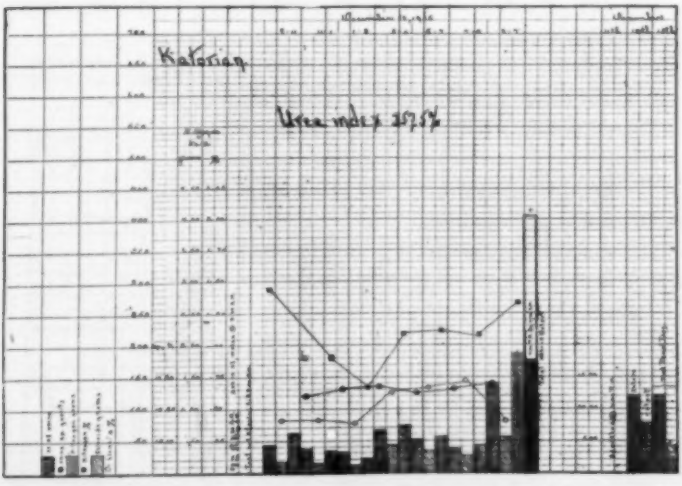

Fig. 15.—Cardiorenal disease, Case 4, test on December 13. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

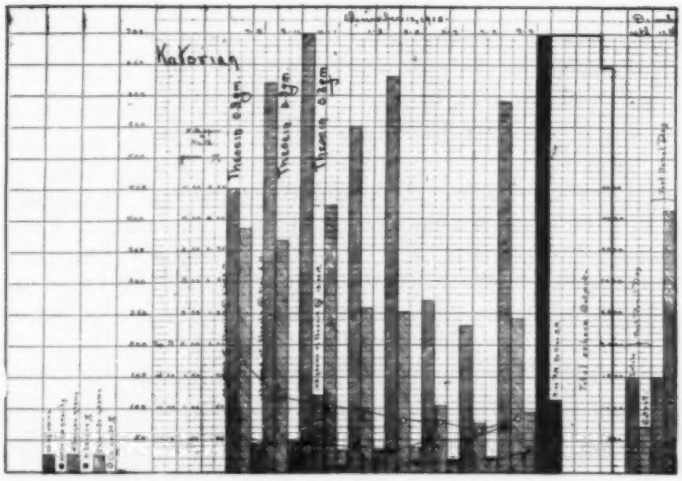

Fig. 16.—Same case as shown in Figure 15, test on December 16. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

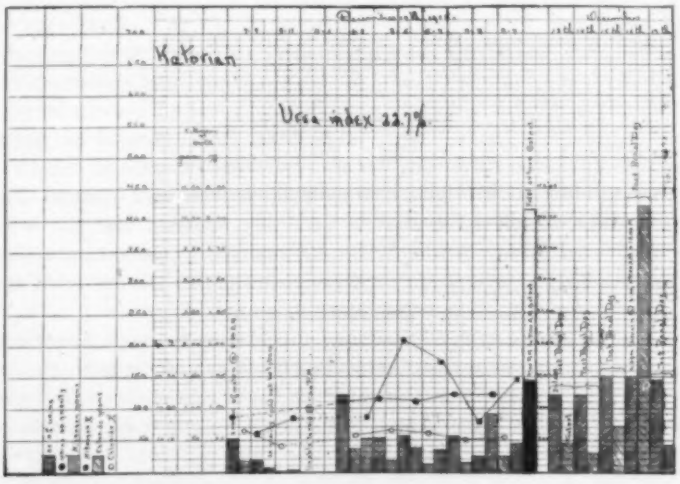

Fig. 17.—Same case as shown in Figures 15 and 16, test on December 17. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

THE TOXIC EFFECTS OF UREA ON NORMAL INDIVIDUALS*

A. W. HEWLETT, M.D., Q. O. GILBERT, M.D.
AND
A. D. WICKETT, M.D.
ANN ARBOR, MICH.

In order to throw light on the nature of uremia, many investigators have studied the physiologic effects produced when urea is administered to or injected into animals. The majority of those who have undertaken such studies were unable to demonstrate that urea acted as a poison. Only a few have succeeded in producing definite toxic effects. For example, Herter and Wakeman,[1] as well as Marshall and Davis,[2] found that approximately 1 per cent. of the body weight must be injected into animals in order to produce a fatal result. Ascoli,[3] in reviewing the earlier literature, has sought to explain the occasional toxic effects observed on one or more of the following assumptions: (1) the urea used was not pure, (2) it was injected intravenously in too concentrated a solution, or (3) where used in dilute solution the effects were attributable to the excessive amounts of liquid rapidly introduced into the body. Under any circumstances it is clear that in animal experiments definite toxic effects can be produced only when extraordinarily large doses of the drug were given, doses which presumably raise the concentration of urea in the body above that which is encountered in most cases of uremia in man. For these reasons the view has become generally accepted that the toxic effects of urea in any concentration encountered in patients are negligible and that the symptoms of uremia are due to the action of the other and more poisonous substances.

Recent advances in our knowledge concerning the toxic symptoms presented by patients in the more advanced stages of nephritis permit one, however, to approach this question from a new point of view. It seems established that uremia, in the sense of any toxic state com-

* Submitted for publication June 12, 1916.
* From the Department of Internal Medicine, University of Michigan.

1. Herter, C. A., and Wakeman, A. J.: On Alterations in the Composition of the Blood Resulting from Double Nephrectomy, Jour. Exper. Med., 1899, iv, 117.

2. Marshall, E. K., Jr., and Davis, D. M.: Urea: Its Distribution in and Elimination from the Body, Jour. Biol. Chem., 1914, xviii, 53.

3. Ascoli, G.: Vorlesungen über Urämie, Jena, 1903, p. 130.

plicating renal disease, includes a variety of distinct conditions. In certain patients, toxic symptoms occur when the urea and the total incoagulable nitrogen of the blood are either not increased or are increased to such a small extent that the symptoms observed can hardly be attributed either to the urea or to an increase in the total incoagulable nitrogen of the blood. This appears to be particularly true of those cases of uremia in which generalized epileptiform convulsions dominate the symptomatology. In such cases particularly, the search for a specific toxic substance seems indicated, and N. B. Foster[4] has reported the isolation of a toxic base from the blood of patients suffering from the convulsive form of uremia.

On the other hand, it has been shown that during the later stages of nephritis there is not infrequently an increase of urea and of other nitrogenous substances, such as uric acid, creatin, creatinin, and indican in the blood and that when this increase becomes very marked toxic symptoms are present. In such patients the urea not only shows the greatest absolute increase, but its increase is relatively greater than the increase in the sum total of the other nonprotein nitrogenous bodies. Clinical studies have demonstrated furthermore that such patients frequently do not present certain of the classic uremic symptoms. Generalized convulsions, paralyses and prolonged comas are often absent. The symptoms which characterize the advanced stages of nitrogenous retention have been for some years the subject of study, particularly by French clinicians. According to Widal,[5] for example, the symptoms consist of loss of appetite, fatigue, prostration, mental dulness, somnolence and eventually coma. Reiss,[6] who has recently described this condition as the asthenic type of uremia, believes that it is characterized clinically by drowsiness and indifference, by bodily fatigue and prostration, and by sudden cardiac death without prolonged coma.

The modern blood studies on nephritic patients have also served to define the relation that exists between the clinical symptoms and the level of urea and nonprotein nitrogen in the blood. While it is difficult, by reason of individual variations, to fix accurately the level at which the accumulation of nitrogenous waste products leads to the production of symptoms, nevertheless one may say in general that symptoms characteristic of asthenic uremia are rarely well defined when the concentration of urea in the blood is less than 100 mg. per

4. Foster, N. B.: The Isolation of a Toxic Substance from the Blood of Uremic Patients, Tr. Assn. Am. Phys., 1915, xxx, 305.

5. Widal, F., and Lemierre, A.: Die diätetische Behandlung der Nierenentzündungen, Ergebn. d. inn. Med. u. Kinderh., 1909, iv, 523.

6. Reiss, E.: Zur Klinik und Einteilung der Urämie, Ztschr. f. klin. Med., 1914, lxxx, 97, 424, 452.

TABLE 1 (EXPERIMENT 1, A. W. H., DEC. 23, 1915).—EFFECT OF INGESTION OF 100 GM. UREA IN ONE DOSE

Time	Urea Taken, Gm.	Urine Passed, C.c.	Rate of Diuresis, 24 Hr., C.c.	Urea per 100 C.c. Urine, Gm.	Urea Excreted, Gm.	Rate of Urea Excretion 24 Hr., Gm.	Urea in Blood, Gm. per 100 C.c.	Ambard	Hb., per Cent.	Remarks
9:26 to 10:02 a. m.	...	21.8	870	3.02	0.66	26.3	0.040	0.074	93	
10:05 to 10:18	100									Considerable nausea
10:02 to 10:37	...	77.7	3,200	2.37	1.84	75.8	(0.072)*			
10:37 to 11:09	...	230	10,350	2.44	5.61	252.54	0.147	0.093	87	11:00, slight headache, stupor, sleepy, nausea less
11:09 to 11:29	...	134	9,650	2.5	3.35	241.25	(0.106)	.....	..	11:12, headache, dizzy; 11:15, headache worse; blood pressure, 120 and 86
11:29 to 12:02	...	240	10,470	2.06	6.38	278.5	0.2	0.118	77	11:30, headache, dizzy; 11:36, soft stool, weak, dizzy; 11:57, headache
12:02 to 12:30	...	158	8,130	2.56	4.04	208	(0.167)	.....	..	12:30, diarrheal stool; better but still headache
12:30 to 1:00 p. m.	...	192	9,220	2.96	5.68	272.9	(0.193)	.....	..	1:00, headache and weak
1:00 to 1:30	...	127	6,100	3.35	4.24	204	(0.168)	.....	..	
1:30 to 2:07	...	161	6,270	3.77	6.07	236.4	0.16	0.107	72	Feel fairly comfortable, but unable to work
2:07 to 3:10	...	267	6,100	3.52	9.4	215	(0.167)	.....	..	Unable to do customary work during the late afternoon

* The amount of urea in the blood when enclosed in parentheses in this and the followng tables was estimated by the method described in the text.

100 c.c. of blood and that they are rarely absent when the concentration exceeds 200 mg. From clinical observations, therefore, one would be inclined to place the point at which the accumulation of urea might possibly cause symptoms between the two limits of 100 and 200 mg. of urea per 100 c.c. of blood.

The bodily and mental prostration which characterizes the earlier stages of asthenic uremia may readily escape detection in animal experiments. For this reason it seemed a matter of some importance to study once again the toxic effects of this compound, using men as the subjects of the study. Our experiments were therefore undertaken with the view of ascertaining whether normal persons manifest toxic symptoms when sufficient urea has been taken by mouth to raise the urea in the blood to the levels encountered in asthenic uremia. Since urea diffuses rapidly from the blood into the tissues, it is evident that in order to attain such concentrations in the blood large quantities of urea must be given. Furthermore, since urea is rapidly eliminated from the body by way of the urine, it is evident that the large quantity of urea must be taken within a brief period of time and that prolonged experiments can be carried out only with considerable difficulty. As will appear in the following experiments, the ingestion of 100 gm. of urea within a few hours raises the level of blood urea in a normal individual to from 150 to 245 mg. per 100 c.c. Such concentrations are comparable with those encountered in the asthenic type of uremia and if the symptoms in the latter condition are in any way dependent on the concentration of urea in the blood and tissues, symptoms should occur under the conditions of our experiment.

Outline of Experiments: Five experiments were performed, four on the authors themselves and one on Dr. F. N. Wilson, who volunteered for this purpose. The subject of the experiment presented himself to the clinical laboratory after his usual breakfast and emptied his bladder. The urea content of his blood was determined and this was compared with the output of urea in the urine by the method of Ambard.[7] The subject then took the urea dissolved in water, either in a single dose or in doses divided over a period of from three to six hours. In three instances the intake was completed before the noon meal, while in two others one or more doses were taken after the meal. The successive specimens of urine were collected, measured and analyzed for urea, over a period varying from nine to thirty hours after the beginning of the experiment. The concentration of urea in the blood and the Ambard coefficient were determined on two or more occasions during the afternoon of the experimental day and

7. Ambard, L., and Weill, A.: Les lois numeriques de la sécrétion rénale de l'urée et du chlorure de sodium, Jour. physiol. et pathol. géner., 1912, xiv, 753.

TABLE 2 (EXPERIMENT 2, A. W. H., APRIL 17, 1916).—EFFECT OF INGESTION OF 125 GM. UREA IN FOUR HOURS

Time	Urea Taken, Gm.	Urine Passed, C.c.	Rate of Diuresis, 24 Hr., C.c.	Urea per 100 C.c. Urine, Gm.	Urea Excreted, Gm.	Rate of Urea Excretion 24 Hr., Gm.	Urea in Blood, Gm. per 100 C.c.	Ambard	Hb., per Cent.	Remarks
9:07 to 9:43 a. m.	...	17.5	700	2.82	0.49	19.7	0.036	0.079	94	Weight 164 pounds
9:45	25	...	.....	....	....	.....	.....	.....	..	Slight nausea
9:43 to 10:43	...	134	3,220	2.28	3.06	73.3	(0.072)			
10:49	25	...	.....	....	....	.....	.....	.....	..	Slight nausea
10:43 to 11:43	...	135	3,720	3.14	4.87	116.9	(0.11)			
11:47	25									
11:43 to 12:43	...	202	4,850	3.24	6.56	157.1	(0.142)	.....	..	12:25, slight headache; rumbling in intestines
12:47	25									
12:43 to 1:50 p. m.	...	207	5,740	3.38	9.03	194	(0.173)	.....	..	12:50, diarrheal discharge, headache worse, some dizziness and apathy, disinclined to work; 1:15, headache and apathy; 1:23, headache better, apathy continues, slight drowsiness, little dizzy, weak
1:52	25									
1:50 to 2:23	...	705	8,950	2.95	6.05	204	(0.21)	.....	..	1:52, considerable apathy and stupor, headache gone; 2:08, dizzy, speech thick and difficult to pronounce words distinctly
2:23 to 2:59	...	251	10,040	2.62	6.57	262.6	0.214	0.130	88	2:50, no headache or dizziness; much apathy and inability to work
2:59 to 3:59	...	251	8,470	3.12	10.95	262.7	(0.215)	.....	..	3:05, apathetic and tired; 3:40, apathetic and dull
3:59 to 4:35	...	197	7,880	4.04	7.96	318.4	(0.240)	.....	..	4:00, little headache; no energy; feeling better
4:35 to 5:11	...	150	6,000	3.90	5.85	214	0.192	0.117	85	4:55, as above
5:11 to 6:40	...	208	4,300	3.56	9.48	153.4	(0.156)	.....	..	6:00, feeling fairly well
6:40 to 8:26	...	285	3,530	4.2	11.97	148.5	(0.154)	.....	..	7:30, same
8:26 to 1:40 a. m.	...	405	2,340	4.08	20.2	95.5	(0.117)			
1:40 to 5:20	...	305	1,990	2.98	9.09	59.4	(0.082)			
5:20 to 7:45	...	215	2,130	3.72	8	79.4	(0.091)	.....	..	Morning work went slowly; otherwise felt well
7:45 to 9:37	...	140	1,800	3.79	5.31	68.2	(0.079)			
9:37 to 10:13	...	50	2,000	3.84	1.92	70.8	0.084	0.086		
10:13 to 1:00 p. m.	...	146	1,380	3.69	5.49	46.6	(0.083)	.....	..	Weight 160 pounds
1:00 to 2:55	...	61.5	770	3.05	1.87	23.5	(0.04)			

TABLE 3 (EXPERIMENT 3, Q. O. G., DEC. 27, 1915).—EFFECT OF INGESTION OF 100 GM. UREA IN THREE HOURS

Time	Urea Taken, Gm.	Urine Passed, C.c.	Rate of Diuresis, 24 Hr., C.c.	Urea per 100 C.c. Urine, Gm.	Urea Excreted, Gm.	Rate of Urea Excretion 24 Hr., Gm.	Urea in Blood, Gm. per 100 C.c.	Ambard	Hb., per Cent.	Remarks
10:20 to 10:56 a. m.	...	33	1,320	2.51	0.83	33.1	0.043	0.075	95	Weight 177 pounds
11:00	25	...	.....	....	....	.....	.....	.....	..	11:38, slight nausea, slight headache and dizzy; 11:45, better
10:56 to 12:26	...	231	3,700	3.04	7.02	112.5	(0.098)			
12:00 m.	25									
12:26 to 1:44 p. m.	...	280	5,170	3.52	9.82	182.7	(0.153)	.....	..	12:37, some headache, sleepy, dizziness; somewhat unsteady when attempting to walk or work with hands
1:00	25									
1:44 to 2:15	...	154	7,150	4.02	6.17	287.4	(0.222)	.....	..	1:30, no nausea, more headache, dull, somnolent; 1:40, dull headache, some throbbing in ears and head, stupid
2:00	25									
2:15 to 2:51	...	198	7,720	4.05	7.8	312.9	0.245	0.122	90	2:15, headache worse, no nausea, dizziness about the same
2:51 to 3:40	...	221	6,468	4.34	9.59	281.6	(0 231)	.....	..	2:54, no nausea, dull frontal headache, difficult to concentrate attention, sleepy
3:40 to 4:36	...	261	6,710	4.00	10.44	268.4	(0.218)	.....	..	3:40, headache no worse, but more stupid and sleepy; difficult to do any work
4:36 to 5:22	...	186	5,820	4.99	9.27	290.5	(0.236)	.....	..	5:10, dull headache; restless and irritable; weight 170 pounds
5:22 to 6:04	...	154	5,280	4.03	6.2	212.8	0.187	0.115	81	5:30, headache began to go away, but still an effort to concentrate and to do any work
6:04 to 7:48	...	238	3,290	5.32	12.66	175.4	(0.181)	.....	..	6:30, excessively irritable, but mental processes are slow
7:48 to 10:50	...	396	3,130	4.75	18.75	148.4	(0.156)	.....	..	8:00, feeling better
10:50 to 2:35 a. m.	...	345	2,210	4.13	14.25	91.3	(0.114)			
2:35 to 8:25	...	287	1,180	5.64	16.2	66.6	(0.099)			
8:25 to 10:43	...	78	814	6.43	5.01	52.4	(0 085)			
10:43 to 11:22	...	18.5	683	6.12	1.13	41.8	0.074	0.092	94	
11:22 to 3.45 p. m.	...	137	717	4.84	6.35	34.7	(0.062)			

once on the following morning. No restriction was placed on the exercise taken, the amount of water drunk or the amount or kind of food eaten.

The quantity of urea in the blood and urine was determined by Van Slyke's urease method. In the earlier experiments the final titrations were performed, using alizarin monosulphate as an indicator. At the suggestion of H. H. Willard, however, methyl red was used as an indicator in one experiment (Experiment 2) and was found to give a more definite end reading. The hemoglobin in each specimen of blood drawn was determined by the Autenriech colorimeter. The results of our observations are shown in Tables 1 to 5.

EFFECT ON UREA CONTENT OF THE BLOOD AND URINE

During these observations the amount of urea taken varied from 100 to 125 gm. In the first experiment 100 were taken within fifteen minutes, in the second 125 gm. were taken in 25 gm. doses at hourly intervals, in the third and fourth 100 gm. were taken in a similar manner, while in the fifth experiment 110 gm. were taken during six hours, the major portion being taken during the first three hours.

The effect of the ingestion was apparent in the first specimen of urine subsequently passed. This showed a more rapid diuresis and an increased excretion of urea. The rate of excretion rapidly augmented and reached a maximum within a few hours after the last dose had been taken. It was evident, therefore, that absorption from the gastro-intestinal canal was very rapid. At the height of the experiment the maximum rate of elimination of urea varied in the different experiments from 11 to 14.8 gm. of urea per hour. From this maximum the rate of elimination fell, at first rapidly and then more slowly. At the end of twenty-four hours it had approached but not reached the original rate. The amount of urea excreted within the twenty-four hours was greater than the amount ingested, but in view of the fact that the urea level in the blood had not yet returned completely to the normal at this time, it is fair to assume that the amount excreted in the twenty-four hours was somewhat less than the sum of what had been ingested and what had been formed in the body during this time.

The amount of urea in the blood as determined by direct analysis also reached a maximum within a few hours after the last dose had been taken. This maximum varied from 150 to 245 mg. per 100 c.c. of blood, indicating that we had attained our object of increasing the concentration of urea in the blood to amounts that were comparable with those encountered in the asthenic type of uremia.

According to Ambard, there exists, for any person, a constant

TABLE 4 (EXPERIMENT 4, A. D. W., JAN. 3, 1916).—EFFECT OF INGESTION OF 100 GM. UREA IN THREE HOURS

Time	Urea Taken, Gm.	Urine Passed, C.c.	Rate of Diuresis, 24 Hr., C.c.	Urea per 100 C.c. Urine, Gm.	Urea Excreted, Gm.	Rate of Urea Excretion 24 Hr., Gm.	Urea in Blood, Gm. per 100 C.c.	Ambard	Hb., per Cent.	Remarks
8:30 to 9:08 a. m.	...	90	3,420	1.2	1.08	41	0.04	0.075	93	Weight 141¼ pounds
9:15	25	...	.....	....	....	.....	.....	.....	..	9:15, nausea, passing off in a few minutes
9:08 to 9:44	...	474	18,900	1.2	5.7	227.5	(0.108)			
10:15	25									
9:44 to 10:56	...	384	7,080	2.5	9.6	192.2	(0.128)	.....	..	10:40, feels uneasy; slight headache passing off in a few minutes
11:15	25									
10:56 to 12:08 p. m.	...	323	6,460	2.91	9.4	187.9	(0.149)	.....	..	11:25, rather dopy, head not clear; blood pressure 130 and 94; no nausea
12:15	25									
12:08 to 12:27	...	91	6,890	3.24	2.9	223.2	(0.18)	.....	..	12:15, headache and dizziness; sleepy
12:27 to 1:08	...	171	6,840	3.37	5.7	230.7	0.193	0.118	87	12:45, feels better now; 12:50, lunch; appetite good; nervous; hands unsteady
1:08 to 2:15	...	391	7,820	3.84	15	300.3	(0.223)	.....	..	1:25, dizzy; hands and feet unsteady; head feels heavy
2:15 to 3:27	...	359	7,180	3.6	12.9	258.5	(0.203)	.....	..	2:15, dizzy and unsteady; 3:00, tired physically and mentally; effort required to accomplish anything; 3:15, blood pressure 130 and 86
3:27 to 4:39	...	333	6,660	3.24	10.8	215.8	(0.177)	.....	..	4:15, head still aches; intellect cloudy; thinks slowly; dizziness less marked; feet heavy and drag
4:39 to 5:15	...	314	12,560	2.04	6.4	256.3	0.17	0.112	75	
5:15 to 5:51	...	222	8,880	2.16	4.8	191.8	(0.150)	.....	..	5:40, weight 142¼ pounds
5:51 to 6:35	...	270	8,840	1.88	5.1	166.4	(0.132)	.....	..	..6:15, headache and tired
6:35 to 11:00	...	920	5,000	2.66	24.4	133	(0.125)			
11:00 to 8:00 a. m.	...	556	1,480	4.36	24.2	64.5	(0.094)			
8:00 to 10:05	...	133	1,530	4.36	5.8	66.7	(0.09)			
10:05 to 11:09	...	235	5,290	1.51	3.5	79.9	(0.076)			
11:09 to 11:45	...	161	6,440	0.98	1.53	63.4	0.059	.094	86	

TABLE 5 (EXPERIMENT 5, F. N. W.).—EFFECT OF INGESTION OF 110 GM. UREA IN SIX HOURS

Time	Urea Taken, Gm.	Urine Passed, C.c.	Rate of Diuresis, 24 Hr., C.c.	Urea per 100 C.c. Urine, Gm.	Urea Excreted, Gm.	Rate of Urea Excretion 24 Hr., Gm.	Urea in Blood, Gm. per 100 C.c.	Ambard	Hb., per Cent.	Remarks
8:42 to 9:15 a. m.	...	35.5	1,430	2.66	0.9	37.8	0.036	0.058	95	
9:30	25									
9:15 to 10:30	...	183	3,600	2.74	5.1	100.3	(0.063)	.....	..	9:30, feels well; 9:40, head a little thick
10:25	25									
10:30 to 11:16	...	173	5,410	4.13	7.1	223.5	(0.111)	.....	..	11:45, head a little thick; otherwise well
11:30	20									
11:16 to 12:16 p. m.	...	230	5,520	4.42	10.1	242.9	(0.122)			
12:30	10									
12:16 to 1:00	...	197	6,450	5.52	10.9	355.9	(0.163)	.....	..	12:35, little weak and thick headed; weak and slightly drowsy; 12:52, less sleepy
1:30	10									
1:00 to 1:48	...	181	5,430	4.33	7.8	235.1	(0.128)	.....	..	1:48, feels well
2:30	10									
1:48 to 2:49	...	248	5,860	4.08	10	236.4	(0.133)			
2:49 to 3:29	...	181	6,510	4.18	7.6	272.1	0.150	0.079	85	3:25, slight headache
3:30	10									
3:29 to 4:19	..	225	6,480	2.80	7.7	232.1	(0.138)	.....	..	4:02, headache
4:19 to 4:59	...	179	6,440	4.14	7.4	266.6	(0.141)			
4:59 to 6:33	...	267	5,620	3.07	12.3	205.3	0.117)			
6.33 to 8:28	...	422	5,380	3.89	16.4	209.5	(0.114)	.....	..	Headache increased until 8:30, at which time it was quite severe; went to sleep and headache passed off during night
8:26 to 6:30 a. m.	...	664	1,640	5.83	39.9	95.6	(0.091)			
6:30 to 9:30	...	122	1,120	5.22	7	89.6	(0.044)			
9:30 to 9:45	...	23	1,320	5.57	1.3	73.5	(0.045)			
9:45 to 10:21	...	34	1,360	4.54	1.5	61.7	0.039	0.042	95	

relation between the concentration of urea in the blood and its excretion in the urine. Ambard's formula is as follows:

$$k = \frac{U}{\sqrt{D\sqrt{\frac{C}{25}}}}$$

in which U represents the number of grams of urea in 1,000 c.c. of blood, D the output of urea over the observed period calculated for twenty-four hours, and C the concentration of urea in the urine excreted, expressed in grams per liter. In the above experiments the Ambard factor k was determined for each specimen of blood drawn. It was found to vary far less than any of the other data that enter into it, that is, the concentration of urea in the blood, the rate of excretion of urea and the diuresis. Nevertheless, the factor did not remain constant in any of the experiments, but regularly showed a rise when the urea concentration in the blood rose and a fall when the urea concentration in the blood fell. One might be inclined to interpret the rise of the Ambard factor during our experiments as an indication of renal fatigue, owing to the extraordinary strain placed on the kidney in the way of excreting urea. Against this interpretation, however, is the fact that the Ambard factor regularly fell during the afternoon of the experiment, although one would expect that here if anywhere the kidney would show signs of fatigue, owing to the continued excessive work. It seems to us probable therefore that the Ambard "constant" is but an approximation to the actual facts and that the kidney does not work with the mathematical precision that might be assumed from such a formula.

Nevertheless, we found the Ambard formula of considerable service in that by this means we were able to estimate the approximate concentration of urea in the blood at numerous points of our experiment. These estimations were made as follows. The determined points on the Ambard curve were connected by straight lines and the Ambard factor was assumed to correspond to the point at which these connecting lines crossed the time intervals. Having this assumed constant and knowing the rate of diuresis and the rate of urea elimination in the urine, we were able to estimate the approximate level of urea in the blood according to the following transposition of the Ambard formula:

$$U = k\sqrt{D\sqrt{\frac{C}{25}}}$$

in which the letters have the same significance as in the original formula. In this way the approximate level of blood urea could be interpolated at numerous points during an experiment. In the tables

these interpolations have been enclosed in parentheses. The advantage of such interpolations is at once obvious when one endeavors to compare the onset and duration of symptoms with the concentration of urea in the blood at different times during an experiment.

EFFECT ON WATER METABOLISM

No restriction of fluid intake was carried out in these experiments and with one exception (Experiment 3) the fluid intake was not recorded. Although it was not possible to follow accurately the water metabolism in the body, nevertheless our observations indicate that the ingestion of such large quantities of urea is not without an effect on the fluids of the body. Considerable thirst was experienced during and for a time after the ingestion of the urea, and as the subjects were allowed to drink freely, considerable water was taken to satisfy this thirst. At the same time a marked diuresis accompanied the elimination of the large quantities of urea. The body weight varied according to the balance between the intake and the output of fluid. In Experiment 4 the subject drank very large quantities of water and gained ½ pound during the day and lost 1½ pounds during the following night. In Experiment 3 the subject lost 7 pounds between the onset of the experiment and 5 o'clock in the afternoon. In Experiment 2, 4 pounds were lost in twenty-four hours and the original weight was not recovered for about four days. The changes in body weight were not recorded in Experiments 1 and 5.

TABLE 6.—EFFECT ON THE HEMOGLOBIN

Experiment	Hemoglobin Before, per Cent.	Hemoglobin After, per Cent.	
		Same Day	Next Morning
1	93	87, 77, 72	92
2	(93)	81, 85	
3	95	90, 81	94
4	93	87, 75	88
5	95	85	95

During each experiment there occurred a definite fall in the hemoglobin, as is shown in Table 6. This fall was usually most pronounced late in the afternoon of the experimental day, when the concentration of urea in the blood had already begun to fall. On the following morning the hemoglobin had returned more or less completely to the normal. Such a transient reduction in the hemoglobin indicates a dilution of the blood and since it also occurred even when the subject was rapidly losing weight (Experiment 3), the necessary liquids in such a case must have been withdrawn from the tissues. This dilution

of the blood during the diuresis following these excessive quantities of urea is perhaps comparable to that which may occur after the ingestion of sodium chlorid or the saline diuretics. It probably played some part in provoking the diuresis in our experiments.

THE SYMPTOMS

Each subject noted his symptoms as they occurred. By comparing these notes with the concentration of urea in the blood at the time, it was possible to add to the objective character of the experiments and to determine to what extent the symptoms corresponded with an augmented concentration of urea in the blood. Experiment 5 differed from the first four, partly because the urea concentration did not reach the same high level and partly because the symptoms were less marked and not so definitely related to the maximum concentration of urea in the blood. For this reason it will be considered separately.

In all of the first four experiments some nausea was experienced after taking the first dose of urea, but vomiting did not occur. The nausea was most marked in Experiment 1, in which 100 gm. of urea were taken within fifteen minutes. In Experiment 2 it was present after the first three doses and was absent after the last two. In Experiments 3 and 4 slight nausea was experienced after the first dose, but none after the next three. In all cases the nausea had disappeared before the concentration in the blood had reached its maximum. It is evident therefore that in these experiments the nausea did not depend on a high concentration of urea in the body fluids or tissues, but was probably associated with local changes in the gastrointestinal canal. The subject of Experiments 1 and 2 had diarrheal evacuations of the intestines a few hours after the ingestion of the urea. The other subjects experienced no intestinal disturbances.

In each of the first four experiments definite symptoms occurred at the time that the concentration of urea in the blood was highest. Headache was first noted, the sensation usually being described as a tight feeling in the head or as a dull ache. This headache was soon followed by dizzy sensations, which were in turn followed by apathy, drowsiness and an inability to do the customary amount of work. Feelings of bodily fatigue and weakness occurred in each case. The subjects of Experiments 3 and 4, on whom fell the burden of the chemical determinations, were in each case unable to carry on this work during the afternoon which followed the taking of the urea, by reason of mental and bodily fatigue, together with an inability to concentrate the attention. In both instances the hands were unsteady. The subject of Experiment 3 became excessively irritable during the afternoon, while the subject of Experiment 4 complained particularly of bodily fatigue. In Experiment 2 at the height of the intoxication the subject found some difficulty in pronouncing words distinctly.

These cerebral and bodily symptoms were most pronounced at the time of maximum concentration of urea in the blood. In all cases they appeared in a definite form at about the time that the blood urea reached a concentration of 150 to 160 mg. per 100 c.c. It is noteworthy that they appeared to be less intense at corresponding levels during the afternoon, when the amount of urea in the body was lessening.

The subject of Experiment 5 did not show so high a concentration of blood urea as did the other subjects. This was due in part to the fact that his ingestion of urea extended over a longer period. In part it was due to the fact that he showed an unusually rapid excretion, with an unusually low Ambard coefficient (increased renal permeability to urea). This subject complained at first of feeling somewhat thick headed, and later of being somewhat drowsy and disinclined to work. The latter symptoms coincided with the maximum concentration of urea in his blood (163 mg.). During the afternoon a headache developed, which gradually became more marked as the afternoon advanced and was quite intense at bedtime. During the night it disappeared. This subject suffers from occasional headaches (migraine?) and the experiment seems to have induced a headache of the usual type, but one of unusual severity. This headache was not due directly to the high concentration of urea in the blood, for it reached its maximum after the concentration in the blood had fallen below 114 mg.

In two experiments (1 and 4) the blood pressures were taken at the height of the intoxication, but in neither case was any marked hypertension present.

The symptoms observed at the maximum concentration of urea in the blood during our experiments correspond almost exactly with those described by Reiss for the asthenic type of uremia, that is, drowsiness and indifference, bodily fatigue and prostration. The loss of appetite described by Widal did not occur. On the other hand, headache and dizziness were quite constant. The symptoms observed developed at approximately the same level of blood urea in all subjects and this level corresponded roughly to that which is associated with definite and unmistakable symptoms in asthenic uremia.

To the analogy that has been drawn between the symptoms observed in these experiments and those of asthenic uremia, the objection might be raised that the symptoms observed after ingestion were due to the rapid entrance of urea into the tissues and that had the high level been maintained for some time the symptoms would have disappeared. This criticism is supported by the fact that the symptoms were usually more marked at a given level of blood urea when the urea was accumulating in the body than they were at the same level

of blood urea when the urea in the body was lessening. It seems probable, therefore, that a portion of the symptoms observed may have been due to the acute character of the experiment. Nevertheless, the following facts indicate that the high level of urea in the body was responsible for the major portion of the symptoms. First, no definite symptoms occurred while the blood urea was rising from 40 to 150 mg. per 100 c.c., nor have symptoms been observed by other observers when from 20 to 30 gm. of urea have been given in a single dose. Second, the onset of symptoms occurred in each of our subjects when the level of blood urea had passed a definite point (about 150 mg.). Third, the symptoms, though less marked, persisted until the blood urea had fallen to approximately 160 mg. per 100 c.c. For these reasons we believe that the symptoms in our experiments were due, in the main, not to the sudden entrance of urea into the tissues, but to its high concentration therein.

It seems probable, therefore, that when as a result of nephritis the blood urea exceeds a concentration of 150 mg. per 100 c.c., the symptoms of bodily and mental asthenia may be explained in part as being due to the high concentration of urea in the body fluids and tissues. This by no means excludes the possibility that other substances may play a rôle in producing the symptoms of this type of uremia and indeed the fact that animals die only when extraordinary doses of urea are administered suggests that the fatal outcome of asthenic uremia in man may be due to other substances than urea.

DISTRIBUTION OF UREA TO THE TISSUES

It is well known that urea diffuses readily between the blood and the tissues. This fact is also apparent in our experiments. Assuming, for example, that there are 5 liters of blood in the body and that all of the urea administered remained in the blood, it would require but 10 gm. of urea to give a concentration of 200 mg. per 100 c.c. of blood. Since approximately 100 gm. of urea were required to raise the blood urea to this level, it is evident that the major portion of the urea absorbed from the gastro-intestinal canal must have passed rapidly from the blood into the tissues.

One may estimate roughly the additional amount of urea in the body at any time during our experiments, for this will equal the amount absorbed from the intestinal canal plus that formed by metabolism in the body and minus that eliminated through the excreta. For purposes of calculation we have assumed (1) that the urea was completely absorbed from the intestinal canal, (2) that it was eliminated entirely by way of the urine and (3) that the rate of metabolism was such that 1.5 gm. of urea were formed hourly in the body. If these assumptions are made, then the total amount of urea in the body

at any time during the experiment may be estimated. Such estimations are shown in Table 7.

The various possible errors in the assumptions on which these calculations are based do not permit one to draw any definite conclusion as to the exact relation that exists between the amount of urea in the body and its concentration in the blood. It should be noted, however, that in the first two experiments diarrheal discharges occurred and that in this way a certain amount of urea was probably lost from the body. If this were the case, the estimated amount of urea in the body would have been less and the relation (*c*) would have been greater. Similarly, in Experiment 5 and in the first estimation of Experiment 4 the blood was drawn about half an hour after the last dose of urea had been given. If one were to assume that this had not been entirely absorbed the excess in the body would again be less and the relation (*c*) greater. It would appear, therefore, that for every gram of excess urea in the body the concentration of urea in the blood rose at least 2.5 mg. per 100 c.c. of blood.

TABLE 7.—Excess Urea in the Body and Its Relation to the Excess in the Blood

Experiment	Body Weight, Kg.	Time Since First Determination, Hours	Excess Urea in Body, Gm. (*a*)	Excess in Blood, Mg. (*b*)	Relation *b* to *a* (*c*)
1	75	2	80	160	1.8
		4	72	120	1.7
2	75	5	98	178	1.8
		7½	77	156	2.0
3	80	4	79	202	2.8
		7	47	144	3.1
4	65	4	76	153	2.0
		8	36	130	3.6
5	78	6	54	113	2.1

If 1 gm. of urea be uniformly distributed in a body weighing 70 kg. it would cause an increase of concentration amounting to 1.4 mg. per 100 gm. It is evident, therefore, that while the major portion of the urea ingested entered the tissues, its concentration in the body as a whole fell considerably short of its concentration in the blood. Marshall and Davis[2] have shown by chemical analyses that the urea concentration in certain organs and tissues of the body is approximately equal to its concentration in the blood. They found, however, that in the case of fat the urea concentration was low, and it seems probable that the same is true of the bones, the cartilages and possibly of other tissues. If one could allow for the low percentages in such

tissues the urea concentration in the remaining tissues of our subjects may have approached that of the blood.

CONCLUSIONS

1. By giving approximately 100 gm. of urea by mouth over a short interval of time it is possible to increase the concentration of urea in the blood of normal persons to levels of from 160 to 245 mg. per 100 c.c.

2. At such levels of blood urea definite symptoms occur. These consist of headache, dizziness, apathy, drowsiness, bodily weakness and fatigue.

3. These symptoms are comparable to those encountered in the asthenic type of uremia.

4. For every gram of excess urea in the body there is a rise of concentration in the blood which approximates 2.5 mg. per 100 c.c.

THE RELATION OF RECURRENT ATTACKS OF PELLAGRA TO RACE, SEX AND AGE OF THE PATIENT AND TO TREATMENT OF THE DISEASE*

J. F. SILER, M.D.
Major Medical Corps, U. S. Army

P. E. GARRISON, M.D.
Passed Asst. Surg., U. S. Navy

AND

W. J. MacNEAL, M.D.
NEW YORK

INTRODUCTION

In the immediately preceding papers of this series[1] we have presented a study of the initial attacks of pellagra observed in Spartanburg County, S. C., up to the end of 1914 and a study of the subsequent history of the survivors of the initial attack. In the present paper we purpose to present a study of the correlation between recurrence of the disease, or escape from recurrence, on the one hand, and race, sex and age of the patient and treatment of the disease, on the other hand. It is expected that this study may contribute to the elucidation of the general question of prognosis in pellagra.

THE RELATION OF RECURRENT ATTACKS OF PELLAGRA TO RACE AND SEX

Of the 971 recorded cases of pellagra with onset previous to 1914, there were 157 patients who died in the year of the initial attack, leaving 814 survivors. Of these patients, 521 were white female pellagrins, 218 were white male pellagrins, one was a white child whose sex was not recorded, sixty were colored female and fourteen were colored male pellagrins. Previous to 1908 there were only six recorded cases in negroes, five females and one male. The latter, as well as three of the negro female pellagrins, died during the year of onset. One of the colored females, Pellagrin 406, had her first attack in 1903 and recurrent attacks in 1904, 1905, 1906 and 1907, dying in

* Submitted for publication June 17, 1916.
* From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.
* This paper has been written since Dr. Garrison and Dr. Siler were recalled to active duty in the Medical Corps, U. S. Navy and U. S. Army, respectively. They are not personally responsible for the detailed compilation of data or for the specific deductions drawn from them.
1. Siler, Garrison and MacNeal, THE ARCHIVES INT. MED., 1916, xviii, 173; Ibid., 1916, xviii, 340.

1907. The other colored female, Pellagrin 1212, had her first attack in 1905 and recurrent attacks every year to 1911, when she died in a recurrent attack. Table 1 shows the sum of all recurrences, deaths in recurrence, years without recurrence, deaths without recurrence and years without definite record for each annual group of incident cases, according to race and sex, the history of one case for one year being the unit in each instance.

In the group of white female pellagrins there were 1,113 instances in which the record of recurrence or nonrecurrence is clear. Of these 695, or 62.4 per cent., suffered recurrences, and in 418, or 37.6 per cent., there was freedom from recurrence. In the group of white males, out of 445 definite records there were 281, or 63.1 per cent., with recurrence and 164, or 36.9 per cent., without recurrence. The agreement between these two groups in this respect was therefore remarkably close. In the group of colored females, out of ninety-eight instances of definite records in years subsequent to the year of onset, there were sixty-eight recurrences, 69.4 per cent., and thirty instances of freedom from recurrence, or 30.6 per cent. of the total instances of definite record. In the group of colored males, out of fourteen pellagrins with definite records in years subsequent to that of the initial attack, a recurrence was observed in nine, or 64.3 per cent., and freedom from recurrence was observed in five, or 35.7 per cent. The data here tabulated indicate, therefore, that, on the whole, surviving pellagrins in Spartanburg County have suffered recurrences of pellagra in the following years almost twice as frequently as they they have escaped the recurrence, and that there has been no very considerable difference in this respect between the various racial or sex groups. There was, however, a very slightly greater tendency for pellagra to recur in the negro survivors than in the survivors of the white race, the recurrence frequency being 69.4 and 64.3 per cent. for female and male negroes, respectively, as against 62.4 and 63.1 per cent. for female and male whites, respectively. This close agreement is really quite remarkable when compared with the very definite differences in behavior of pellagra in other respects in its relation to race and sex.

The deaths during the year of recurrent attack were sixty-five out of 695 recurrences in white females, representing a death rate of 9.4 per cent., forty-two out of 281 recurrences in white males, a death rate of 14.9 per cent.; for colored females, nineteen deaths in sixty-eight recurrences, a death rate of 27.9 per cent.; for colored males, four deaths in nine recurrences, a death rate of 44.4 per cent. The death rates, therefore, show a marked variation, dependent on race and sex, and this variation is quite similar to that shown by death

TABLE 1.—Summary of Subsequent History of the 814 Pellagrins Who Survived the Initial Attack, According to Race and Sex and According to Year of Onset

	Year of Onset							
	Before 1908	1908	1909	1910	1911	1912	1913	Sum
Female, white—								
Incident pellagrins in group	39	17	37	93	140	115	154	595
Deaths in year of onset	8	2	7	16	18	12	11	74
Survivors of initial attack	31	15	30	77	122	103	143	521
Subsequent recurrences	112	42	57	153	178	83	67	695
Deaths in recurrence	13	3	9	17	17	4	2	65
Years without recurrence	40	20	42	78	121	76	41	418
Deaths without recurrence	4	1	2	5	3	4	1	20
Years with uncertain record	44	7	15	27	34	37	34	198
Male, white—								
Incident pellagrins in groups	12	2	16	30	68	67	59	254
Deaths in year of onset	1	0	6	7	6	6	10	36
Survivors of initial attack	11	2	10	23	62	61	49	218
Subsequent recurrences	71	8	25	41	60	57	19	281
Deaths in recurrence	7	1	4	7	11	11	1	42
Years without recurrence	15	0	0	25	72	36	16	164
Deaths without recurrence	1	0	1	1	1	1	2	7
Years with uncertain record	8	1	7	6	37	21	12	92
Female, colored—								
Incident pellagrins in group	5	1	3	15	19	24	25	92
Deaths in year of onset	3	0	2	4	6	6	11	32
Survivors of initial attack	2	1	1	11	13	18	14	60
Subsequent recurrences	10	6	2	18	17	9	6	68
Deaths in recurrence	2	0	1	6	7	3	0	19
Years without recurrence	0	0	0	4	10	12	4	30
Deaths without recurrence	0	0	0	0	2	2	1	5
Years with uncertain record	0	0	0	7	1	9	3	20
Male, colored—								
Incident pellagrins in group	1	0	1	3	6	5	13	29
Deaths in year of onset	1	0	1	1	3	3	6	15
Survivors of initial attack	0	0	0	2	3	2	7	14
Subsequent recurrences	0	0	0	2	3	1	3	9
Deaths in recurrence	0	0	0	1	2	0	1	4
Years without recurrence	0	0	0	0	3	1	1	5
Deaths without recurrence	0	0	0	1	0	1	1	3
Years with uncertain record	0	0	0	0	0	0	2	2

rate in the initial attack, considered in a preceding paper of this series. The comparative figures are shown in Table 2. The similarity between death rate in initial attack and death rate in recurrent attack is rather striking. In each instance, except for the group of white males, the death rate in recurrence is slightly lower than the death rate during the year of onset.

TABLE 2.—Mortality Rate in Initial Attacks and in Recurrent Attacks of Pellagra for Each Race and Sex, Per Cent., for 971 Cases with Onset Before 1914

	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Initial attack	12.4	14.2	13	34.8	51.7	38.8	15.4	18	16.2
Recurrent attack	9.4	14.9	11	27.9	44.4	29.9	11	15.9	12.3

Attention may be directed to the fact that the white race, in which the incidence of pellagra was much higher, was the one to show the lower death rate in initial attack, lower recurrence rate among survivors and lower death rate in recurrence; furthermore, the females of each race, groups in which the incidence rate of pellagra was relatively much higher than in the males, show the lower death rate in the year of onset, almost equal recurrence rate in subsequent years and lower death rate in recurrence. If, therefore, we consider death rates and recurrence rates to depend on general vigor, condition of nutrition and available diet, it seems somewhat difficult to account for the relative incidence rates without taking into account some additional factor.

RELATION BETWEEN RECURRENCE AND AGE AT ONSET OF PELLAGRA

In our series of 1,180 cases of pellagra there were fourteen with onset of the disease before the age of 2 years had been attained. These cases have been fully considered in the fifth paper of this series[2] in which their histories were presented in detail. Of the fourteen patients, one, the only negro in the group, died in the initial attack of pellagra. Five of the little pellagrins were white girls, three with onset of pellagra in 1914, one with onset in 1909 and one in 1911. The latter died early in 1912 without recurrence. The former suffered recurrence in 1910, the second year, and escaped without recurrence in 1911, 1912, 1913 and 1914. Eight of the pellagrous infants were white boys, six of them with onset before 1914. The subsequent

2. Footnote 1, first reference.

TABLE 3.—SUMMARY OF THE SUBSEQUENT HISTORY OF THE 814 PELLAGRINS WHO SURVIVED THE YEAR OF INITIAL ATTACK PREVIOUS TO 1914

Age at Onset, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Subsequent years with recurrence:									
0 to 4	26	23	49	0	0	0	26	23	49
5 to 9	23	28	51	4	0	4	27	28	55
10 to 14	11	7	18	0	0	0	11	7	18
15 to 19	66	5	71	10	2	12	76	7	83
20 to 29	276	15	291	24	5	29	300	20	320
30 to 39	161	46	207	21	1	22	182	47	229
40 to 49	77	47	124	6	0	6	83	47	130
50 to 59	43	59	102	1	1	2	44	60	104
60 to 69	8	45	53	0	0	0	8	45	53
Over 70	1	6	7	0	0	0	1	6	7
Age unknown	3	0	3	2	0	2	5	0	5
Total	695	281	976	68	9	79	763	290	1,053
Deaths in year of recurrence:									
0 to 4	0	1	1	0	0	0	0	1	1
5 to 9	1	1	2	1	0	1	2	1	3
10 to 14	0	0	0	0	0	0	0	0	0
15 to 19	6	0	6	4	1	5	10	1	11
20 to 29	24	3	27	6	1	7	30	4	34
30 to 39	16	6	22	3	1	4	19	7	26
40 to 49	9	13	22	1	0	1	10	13	23
50 to 59	7	11	18	3	1	4	10	12	22
60 to 69	1	4	5	0	0	0	1	4	5
Over 70	0	3	3	0	0	0	0	3	3
Age unknown	1	0	1	1	0	1	2	0	2
Total	65	42	107	19	4	23	84	46	130
Years survived without recurrence:									
0 to 4	28	39	67	0	0	0	28	39	67
5 to 9	28	26	54	0	0	0	28	26	54
10 to 14	7	20	27	0	0	0	7	20	27
15 to 19	31	6	37	6	0	6	37	6	43
20 to 29	128	4	132	18	1	19	146	5	151
30 to 39	113	15	128	3	0	3	116	15	131
40 to 49	72	30	102	1	4	5	73	34	107
50 to 59	7	19	26	0	0	0	7	19	26
60 to 69	3	5	8	0	0	0	3	5	8
Over 70	1	0	1	2	0	2	3	0	3
Age unknown	0	0	0	0	0	0	0	0	0
Total	418	164	582	30	5	35	448	169	617

TABLE 3.—SUMMARY OF THE SUBSEQUENT HISTORY OF THE 814 PELLAGRINS WHO SURVIVED THE YEAR OF INITIAL ATTACK PREVIOUS TO 1914—(*Continued*)

Age at Onset, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Deaths without recurrence in year of death:									
0 to 4	1	0	1	0	0	0	1	0	0
5 to 9	0	0	0	0	1	1	0	1	1
10 to 14	0	0	0	0	0	0	0	0	0
15 to 19	2	0	2	0	0	0	2	0	2
20 to 29	8	1	9	1	0	1	9	1	10
30 to 39	4	0	4	0	1	1	4	1	5
40 to 49	1	1	2	0	0	0	1	1	2
50 to 59	2	2	4	3	0	3	5	2	7
60 to 69	1	2	3	1	1	2	2	3	5
Over 70	1	1	2	0	0	0	1	1	2
Age unknown	0	0	0	0	0	0	0	0	0
Total	20	7	27	5	3	8	25	10	35
Years without definite record:									
0 to 4	5	9	17*	0	0	0	5	9	17*
5 to 9	6	15	21	2	1	3	8	16	24
10 to 14	2	9	11	0	0	0	2	9	11
15 to 19	15	6	21	1	0	1	16	6	22
20 to 29	68	9	77	10	0	10	78	9	87
30 to 39	51	12	63	6	0	6	57	12	69
40 to 49	24	10	34	1	0	1	25	10	35
50 to 59	13	19	32	0	0	0	13	19	32
60 to 69	5	3	8	0	1	1	5	4	9
Over 70	0	0	0	0	0	0	0	0	0
Age unknown	9	0	9	0	0	0	9	0	9
Total	198	92	298*	20	2	22	218	94	315*

* Including the record of one white child, sex unknown, with initial attack in 1911 and indefinite record in 1912, 1913 and 1914.

history of these six patients shows eleven instances of recurrence, one instance of death in recurrence and eight instances of a year without recurrence. The subsequent history of the whole group showed, therefore, twelve instance of recurrence, one instance of death in recurrence, twelve instances of survival of a year without recurrence and one death in a year without recurrence.

There were seventy-two pellagrins, 2 to 4 years of age at the time of onset of the disease, of whom fifty-six had the initial attack before 1914, with two deaths during the year of onset. The subsequent history of the fifty-four remaining patients is summarized along with that of the cases with onset under the age of 2 years in Table 3. In

this table are presented the summarized data in regard to subsequent history for the 814 survivors of the initial attack, according to race, sex and age at onset of the disease, by 5-year age periods to age 20, and after that by decades. There are 521 white females, 218 white males, one white child of unknown sex, sixty negro females and fourteen negro males here considered. The important sections of this table are those showing the years with recurrence, the deaths in recurrence and the number of escapes from recurrence. The data for deaths in a year without recurrence and for years without definite record are also presented in the table for the sake of completeness. The number of these is roughly proportional to the size of the respective groups of survivors of the initial attack. The influence of age at onset on recurrence in subsequent years may be seen by comparing the number of recurrences with the total instances of definite record (that is, the sum of recurrences and escapes from recurrence) shown in the record of each age group and by computing the death rate for the recurrences in each age group. The relative frequency of recurrence for each age group is shown in Table 4. The tendency to recurrence in subsequent years has been distinctly less in white children than in the white adults. The variation between the different groups in this respect is somewhat irregular, but the white girls under 10 years of age at onset of the disease furnished forty-nine instances of recurrence in a total of 105 definite observations, or 46.7 per cent., while in the group with onset between 10 and 20 years of age the recurrences were seventy-seven in a total of 115 definite observations, or 67 per cent., and in the large group of white women with onset of pellagra in the age period from 20 to 59 years, the subsequent record showed 557 recurrences out of 877 definite observations, or 63.5 per cent., so that the prognosis for escape from recurrence was distinctly better in children than in adults. For the white males this distinction between children and adults is even more marked. Of the 116 definite observations in subsequent years for boys who contracted pellagra before the age of 10, only fifty-one were instances of recurrence, or 44 per cent., while the 235 definite records for subsequent years for the men who contracted pellagra between the ages of 20 and 50 years, include 167 instances of recurrence, or 71.1 per cent. The very low recurrence rate (25.9 per cent.) for boys between 10 and 15 years of age at the time of onset is in accord with the evidence previously presented, indicating an increased resistance to pellagra becoming manifest at about this time and continuing for several years in the male sex. For the white women who contracted pellagra after the age of 60 years and survived the year of onset, there were thirteen instances of definite observation in a subsequent year, of which nine

were recurrences and four were escapes from recurrence. The recurrence rate was therefore 69.2 per cent., slightly higher than in the younger women. The white men who contracted pellagra after the age of 60 years furnished fifty-six instances of definite record in sub-

TABLE 4.—Relative Frequency of Recurrence of Pellagra in the Definite Records of the 814 Pellagrins Who Survived the Initial Attack of Pellagra Previous to 1914, Grouped According to Race, Sex and Age at Onset of Initial Attack

Age at Onset of Initial Attack	Female			Male			Both Sexes		
	Total Definite Records	Recurrences		Total Definite Records	Recurrences		Total Definite Records	Recurrences	
		Number	Per Cent.		Number	Per Cent.		Number	Per Cent.
White pellagrins									
0 to 4	54	26	48.1	62	23	37.1	116	49	42.2
5 to 9	51	23	45.1	54	28	51.9	105	51	48.6
10 to 14	18	11	61.1	27	7	25.9	45	18	40
15 to 19	97	66	68	11	5	45.5	108	71	65.7
20 to 29	404	276	68.3	19	15	78.9	423	291	68.8
30 to 39	274	161	58.8	61	46	75.4	335	207	61.8
40 to 49	140	77	51.7	77	47	61	226	124	54.9
50 to 59	50	43	86	78	59	75.6	128	102	79.7
60 to 69	11	8	72.7	50	45	90	61	53	86.9
Over 70	2	1	50	6	6	100	8	7	87.5
Age unknown	3	3	100	0	0	.....	3	3	100
Total	1,113	695	62.4	445	281	63.1	1,558	976	62.6
Colored pellagrins									
0 to 4	0	0	.....	0	0	.....	0	0	.....
5 to 9	4	4	100	0	0	.....	4	4	100
10 to 14	0	0	.....	0	0	.....	0	0	.....
15 to 19	16	10	62.5	2	2	100	18	12	66.7
20 to 29	42	24	57.1	6	5	83.3	48	29	60.4
30 to 39	24	21	87.5	1	1	100	25	22	88
40 to 49	7	6	85.7	4	0	0	11	6	54.5
50 to 59	1	1	100	1	1	100	2	2	100
60 to 69	0	0	.....	0	0	.....	0	0	.....
Over 70	2	0	0	0	0	.....	2	0	0
Age unknown	2	2	100	0	0	.....	2	2	100
Total	98	68	69.4	14	9	64.3	112	77	68.8
Total both races	1,211	763	63.0	459	290	63.2	1,670	1,053	63.1

sequent years, fifty-one of which were recurrences and only five escapes from recurrence. The indicated recurrence rate, 91.1 per cent., is considerably higher than for the younger men.

The figures in regard to tendency for pellagra to recur in the colored pellagrins are of much less value because of the smaller number of observations in this race. On the whole, they seem to be not significantly different from those for the white race.

TABLE 5.—Death Rate in Recurrent Attacks of Pellagra for Each Group According to Race, Sex and Age at Onset of the Initial Attack

Age at Onset of Initial Attack	Female			Male			Both Sexes		
	Recurrent Attacks	Deaths	Rate per Cent.	Recurrent Attacks	Deaths	Rate per Cent.	Recurrent Attacks	Deaths	Rate per Cent.
White pellagrins									
0 to 4	26	0	0	23	1	4.3	49	1	2
5 to 9	23	1	4.3	28	1	3.6	51	2	3.9
10 to 14	11	0	0	7	0	0	18	0	0
15 to 19	66	6	9.1	5	0	0	71	6	8.5
20 to 29	276	24	8.7	15	3	20	291	27	9.3
30 to 39	161	16	9.9	46	6	13	207	22	10.6
40 to 49	77	9	11.7	47	13	27.7	124	22	17.7
50 to 59	43	7	16.3	59	11	18.6	102	18	17.6
60 to 69	8	1	12.5	45	4	8.8	53	5	9.4
Over 70	1	0	0	6	3	50	7	3	42.9
Age unknown	3	1	33.3	0	0	.....	3	1	33.3
Total	695	65	9.4	281	42	14.9	976	107	11
Colored pellagrins									
0 to 4	0	0	.....	0	0	.....	0	0	.....
5 to 9	4	1	25	0	0	.....	4	1	25
10 to 14	0	0	.....	0	0	.....	0	0	.....
15 to 19	10	4	40	2	1	50	12	5	41.7
20 to 29	24	6	25	5	1	20	29	7	24.1
30 to 39	21	3	14.3	1	1	100	22	4	18.2
40 to 49	2	1	50	0	0	.....	2	1	50
50 to 59	5	3	60	1	1	100	6	4	66.7
60 to 69	0	0	.....	0	0	.....	0	0	.....
Over 70	0	0	.....	0	0	.....	0	0	.....
Age unknown	2	1	50	0	0	.....	2	1	50
Total	68	19	27.9	9	4	44.4	79	23	29.1

The death rate in the known recurrences for each group of pellagrins according to age at onset of the initial attack is shown in Table 5. The better prognosis in children is also apparent here in the relatively low mortality in recurrent attack for those under 10 years of age at the onset of pellagra. There were just 100 recorded recurrent attacks in the white children of this age group with only three deaths.

The increased resistance to pellagra at puberty is again indicated by the eighteen recurrences in the group with onset at age 10 to 14, inclusive, with no deaths at all. For those with onset at later years of life the mortality rate in recurrence increases with their age at onset, although irregular fluctuations are present. In the 557 recurrent attacks in white women with onset of pellagra between 20 to 60 years, there were fifty-six deaths, the indicated mortality rate being 10.1 per cent. In the analogous group of white men there were thirty-three deaths in 167 recurrent attacks, indicating a death rate of 19.8 per cent. In the analogous age group of negro women there were thirteen deaths in fifty-two recurrent attacks, a death rate of 25 per cent., and in the similar age group of colored men the death rate was 42.9 per cent., three deaths in seven recurrent attacks. The negro children furnished only four recorded recurrences, all in girls, with one death.

THE RELATION OF SEX AND AGE TO RECOVERY FROM PELLAGRA

A reliable criterion by which to judge recovery from pellagra is not known to us. It nevertheless seems worth while to consider those pellagrins who suffered their initial attack in 1912 or before and have remained free from any recurrence of the disease for two or more years as instances of probable recovery. As has been shown in the preceding paper of this series, it may be expected that a few of these are not really valid recoveries and it will be evident from what follows here that this statement applies especially to the child-bearing women. Nevertheless, a period of at least two years without any recurrence is a definite and sufficiently accurate criterion of recovery for our present purpose, which is to show the relation of recovery to race, sex and age.

The distribution, according to sex and age at onset of the initial attack, of the white pellagrins in this category is shown in Table 6. The significance of these figures will be better appreciated by comparing them with the number of incident attacks of pellagra observed at each age in the years previous to 1913, shown in the fifth paper[2] of this series. This comparison is shown in Table 7 for the 5-year age groups. The tendency to recovery after one attack is distinctly greater in children, no less than thirty, or 34.9 per cent., of the eighty-six pellagrins with onset under the age of 10 years having suffered only the single attack. Of the twelve boys who had their first attack of pellagra in the age period 10 to 14 years, no less than six, or 50 per cent., escaped recurrence of the disease. Of the 478 white pellagrins with onset after the age of 20 years, previous to 1913, only forty-three have remained free from recurrence, giving a recovery

TABLE 6.—White Pellagrins Who Suffered Only One Attack and Have Remained Free from Recurrence for at Least Two Years

Age at Onset	Female	Male	Total	Age at Onset	Female	Male	Total
0	0	0	0	30	2	0	2
1	0	2	2	31	0	0	0
2	2	2	4	32	1	2	3
3	2	1	3	33	2	1	3
4	3	4	7	34	2	0	2
5	1	1	2	35	2	0	2
6	2	4	6	36	0	0	0
7	1	0	1	37	1	0	1
8	2	1	3	38	1	1	2
9	1	1	2	39	1	0	1
10	1	1	2	40	1	0	1
11	0	1	1	41	2	0	2
12	0	1	1	42	2	2	4
13	1	1	2	43	1	0	1
14	0	2	2	44	0	0	0
15	0	0	0	45	1	0	1
16	0	0	0	46	1	0	1
17	3	2	5	47	1	0	1
18	0	0	0	48	0	0	0
19	1	0	1	49	0	0	0
20	1	0	1	50	0	0	0
21	0	0	0	51	0	0	0
22	2	0	2	52	0	0	0
23	2	1	3	53	0	0	0
24	1	0	1	54	0	0	0
25	1	0	1	55	0	1	1
26	2	0	2	56	0	0	0
27	2	0	2	57	0	1	1
28	0	0	0				
29	2	0	2	Total....	54	33	87

TABLE 7.—Proportion of White Pellagrins with Onset Before 1913, Who Have Suffered no Recurrence, Distributed According to Sex and Age at Onset of the Initial Attack

Age at Onset, Years	White Female			White Male			Total White		
	Incident Pellagrins	Without Recurrence		Incident Pellagrins	Without Recurrence		Incident Pellagrins	Without Recurrence	
		Number	Per Cent.		Number	Per Cent.		Number	Per Cent.
0 to 4.....	18	7	38.9	22	9	40.9	41†	16	39
5 to 9.....	20	7	35	23	7	30.4	43	14	32.6
10 to 14.....	9	2	22.2	12	6	50	21	8	38.1
15 to 19.....	37	4	10.8	5	2	40	42	6	14.3
20 to 29.....	135*	13	9.6	13	1	7.7	148*	14	9.5
30 to 39.....	111	12	10.8	24	4	16.7	135	16	11.9
40 to 49.....	57	9	15.8	35	2	5.7	92	11	12
50 to 59.....	30	0	0	37	2	5.4	67	2	3
60 to 69.....	14	0	0	15	0	0	29	0	0
Over 70.....	1	0	0	6	0	0	7	0	0
Age unknown...	10	0	0	2	0	0	12	0	0
Total.....	442*	54	12.2	194	33	17	637*	87	13.7

* Excluding Pellagrin 780, a colored female, who was included in the group of white females by mistake in the fifth paper of this series.
† Including a white child, aged 2 years, whose sex was not ascertained.

rate of 9 per cent. According to this analysis the chance of recovery after one attack is about four times as good in white children under 10 years of age as in white adults over the age of 20 years.

It seems useless to tabulate the data in regard to similar recoveries in negroes, because there are only seven instances in this race. Six of them were colored women with onset at the ages of 18, 20, 22, 22, 23 and 29, and one was a colored man with onset at the age of 48 years.

In a previous paper[3] we have called attention to the recurrence of pellagra after an interval of freedom from attacks of the disease, but in that study it was evident that escape for one year made subsequent recurrence rather unlikely. Among the 720 pellagrins with initial attack previous to 1913, there were twenty-four who escaped recurrence for one year only to suffer recurrence in the following year. Two of these were colored women, ages at onset of initial attack

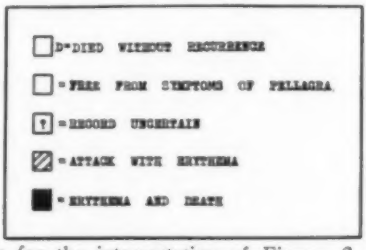

Fig. 1.—Key for the interpretation of Figures 2, 3, 4 and 5.

being 25 years and 34 years. Four were white males, ages at onset of the initial attack being 14, 44, 54 and 56 years. Eighteen were white females, the ages at onset being 5, 7, 16, 21, 22, 24, 24, 26, 26, 26, 30, 30, 32, 34, 35, 36, 39 and 42 years.

Among the 509 pellagrins with initial attack previous to 1912, there were fourteen who escaped recurrence for two consecutive years and then suffered recurrence in the next year. All of them were white females and their ages at onset were 7, 22, 23, 23, 25, 28, 28, 29, 32, 33, 33, 34, 37 and 44 years. The great excess of white women of the child-bearing age in such instances of escape for one or two years with subsequent recurrence suggests that pregnancy and childbirth have an important relation to the phenomenon. We expect to discuss this relationship in a subsequent paper of this series.

In the series of pellagrins there were instances of recurrence (or of new onset?) after much longer intervals of freedom from attack, the longest interval of good health being eighteen years. These instances are not sufficiently numerous to warrant detailed discussion.

Figures 1, 2, 3, 4 and 5 show in detail the behavior during subse-

3. Footnote 1, second reference.

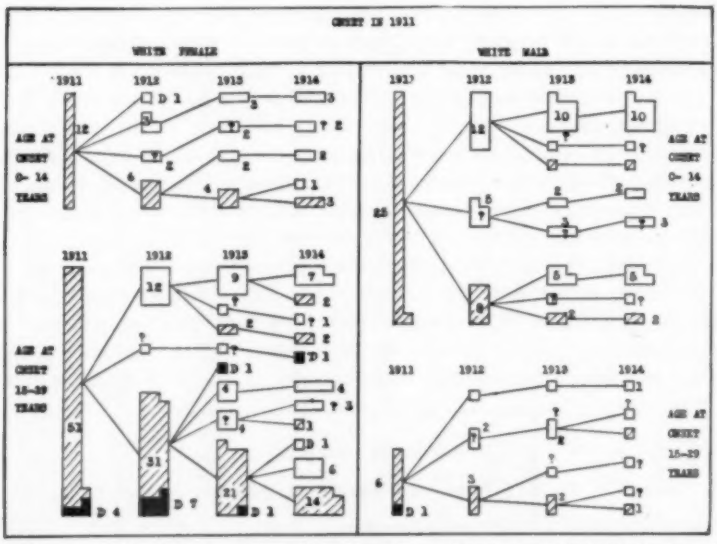

Fig. 2.—Behavior of white pellagrins who suffered their initial attacks of pellagra in 1911 before attaining the age of 30 years, grouped according to sex and age at onset of the initial attack.

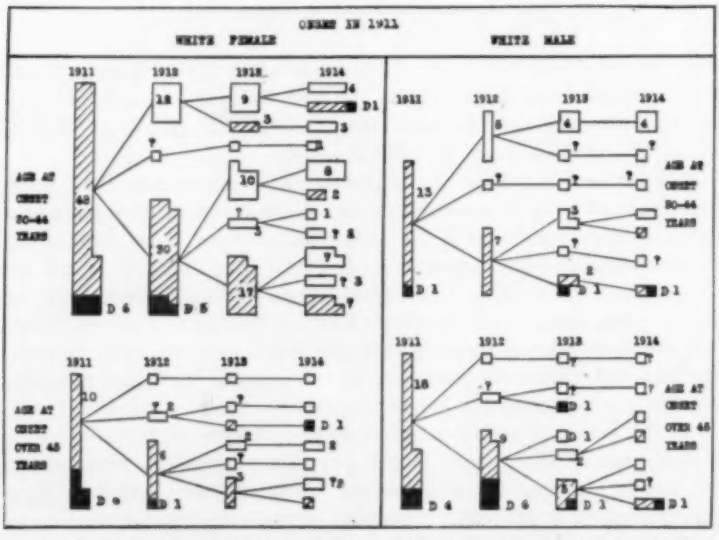

Fig. 3.—Behavior of white pellagrins who suffered their initial attacks of pellagra in 1911 after attaining the age of 30 years, grouped according to sex and age at onset of the initial attack.

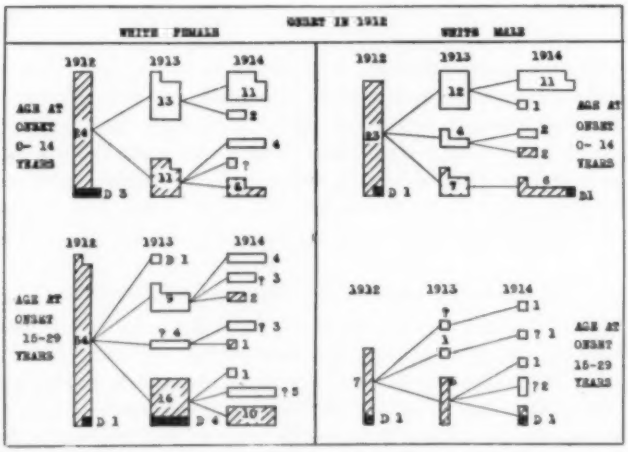

Fig. 4.—Behavior of white pellagrins who suffered their initial attacks of pellagra in 1912 before attaining the age of 30 years, grouped according to sex and age at onset of the initial attack. In the upper groups of this figure are represented two girls and one boy who escaped recurrence in 1913 and were without definite record in 1914. The question mark has been omitted in the 1914 blocks by mistake.

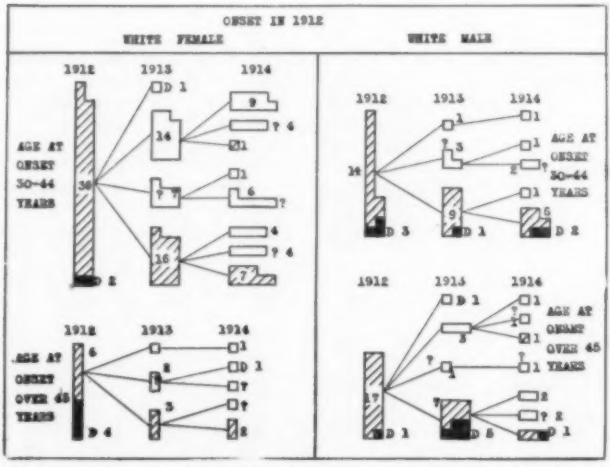

Fig. 5.—Behavior of white pellagrins who suffered their initial attacks of pellagra in 1912 after attaining the age of 30 years, grouped according to sex and age at onset of the initial attack.

quent years of the white pellagrins who suffered their first attacks in 1911 and 1912, by 15-year age groups. These figures indicate more definitely than do the tables the exact nature of the records. Especially noticeable is the low death rate in recurrence for the pellagrins who had their initial attack before the age of 15 and the considerable number of apparent recoveries in these groups. One should also note in the white women of child-bearing age a marked tendency to recurrence after escaping an attack for one year or even longer, which is not so evident in the other groups. The higher death rate in older men is also evident.

THE BETTER PROGNOSIS OF PELLAGRA IN CHILDREN

Table 8 presents in a summarized form for easy comparison the incidence rate of pellagra per 10,000 population, the death rate in year of initial attack, the rate of recovery after one attack, the recurrence rate of the survivors in subsequent years and the death rate in recurrent attack for the white children with onset of pellagra under the age of 10 and for the total white population. The contrast indicates very distinctly the much better prognosis in children, especially in respect to death rate and recovery rate, although they contracted the disease almost as readily as the rest of the population. The contrast is especially definite in the white males, in which group the children show an incidence rate approximately equal to that of the whole group, but their death rate in the year of onset is about one twentieth, their recovery rate more than twice, their recurrence rate a little more than two-thirds and their mortality in recurrence about one fourth that of the whole group.

TABLE 8.—COMPARISON OF WHITE CHILDREN WITH ONSET OF PELLAGRA UNDER 10 YEARS, WITH TOTAL WHITE PELLAGROUS POPULATION IN RESPECT TO INCIDENCE RATE, DEATH RATE IN YEAR OF ONSET, RECOVERY RATE, RECURRENCE RATE AND DEATH RATE IN RECURRENCE OF PELLAGRA

	White Female		White Male		Both Sexes	
	Children	Total Population	Children	Total Population	Children	Total Population
Incidence* per 10,000..	102	231	101	103	102	165
Deaths* in initial attack, per cent.	2.3	11.7	1.1	21.2	1.7	14.1
Recovery after one attack, per cent. ...	36 8	12.2	35.6	17	35.7	13.7
Recurrence rate, per cent.	46.7	62.4	44	63.1	45.2	62.6
Deaths in recurrence, per cent.	2	9.4	2.9	14.9	2	11

* Detailed data will be found in a preceding paper of this series, THE ARCHIVES INT. MED., 1916, xviii, 173.

TABLE 9.—The Distribution of the Total 1,053 Recurrent Attacks of Pellagra According to Age of the Patient at Onset of the Respective Recurrence

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0	0	0	0	0	0	0	0	0	0
1	0	2	2	0	0	0	0	2	2
2	1	4	5	0	0	0	1	4	5
3	3	8	11	0	0	0	3	8	11
4	5	3	8	0	0	0	5	3	8
5	11	5	16	0	0	0	11	5	16
6	6	3	9	0	0	0	6	3	9
7	4	6	10	1	0	1	5	6	11
8	6	8	14	0	0	0	6	8	14
9	6	6	12	0	0	0	6	6	12
10	7	4	11	0	0	0	7	4	11
11	2	4	6	0	0	0	2	4	6
12	2	2	4	1	0	1	3	2	5
13	4	1	5	0	0	0	4	1	5
14	2	0	2	0	0	0	2	0	2
15	1	0	1	0	0	0	1	0	1
16	1	2	3	1	0	1	2	2	4
17	5	1	6	1	0	1	6	1	7
18	10	0	10	2	1	3	12	1	13
19	14	0	14	2	1	3	16	1	17
20	17	2	19	4	0	4	21	2	23
21	16	1	17	1	0	1	17	1	18
22	21	2	23	2	2	4	23	4	27
23	20	2	22	2	2	4	22	4	26
24	24	1	25	2	0	2	26	1	27
25	24	0	24	4	0	4	28	0	28
26	37	3	40	4	1	5	41	4	45
27	37	3	40	2	0	2	39	3	42
28	37	2	39	2	0	2	39	2	41
29	30	1	31	2	0	2	32	1	33
30	24	2	26	2	0	2	26	2	28
31	16	0	16	6	0	6	22	0	22
32	21	1	22	2	0	2	23	1	24
33	20	3	23	2	0	2	22	3	25
34	19	3	22	3	1	4	22	4	26
35	23	4	27	4	0	4	27	4	31
36	20	5	25	3	0	3	23	5	28
37	17	6	23	1	0	1	18	6	24
38	20	8	28	1	0	1	21	8	29
39	8	5	13	1	0	1	9	5	14
40	11	4	15	1	0	1	12	4	16
41	9	4	13	0	0	0	9	4	13
42	11	6	17	1	0	1	12	6	18
43	13	5	18	0	0	0	13	5	18
44	6	7	13	0	0	0	6	7	13
45	13	9	22	0	0	0	13	9	22
46	4	1	5	0	0	0	4	1	5
47	4	3	7	0	0	0	4	3	7
48	4	5	9	0	0	0	4	5	9
49	5	3	8	0	0	0	5	3	8
50	8	5	13	1	0	1	9	5	14
51	7	2	9	0	0	0	7	2	9
52	10	3	13	0	0	0	10	3	13
53	3	4	7	0	0	0	3	4	7
54	6	3	9	2	0	2	8	3	11
55	5	5	10	0	0	0	5	5	10
56	6	5	11	0	0	0	6	5	11
57	3	5	8	1	0	1	4	5	9
58	4	8	12	1	1	2	5	9	14
59	2	8	10	0	0	0	2	8	10

TABLE 9.—THE DISTRIBUTION OF THE TOTAL 1,053 RECURRENT ATTACKS OF PELLAGRA ACCORDING TO AGE OF THE PATIENT AT ONSET OF THE RESPECTIVE RECURRENCE—(*Continued*)

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
60	3	9	12	1	0	1	4	9	13
61	3	6	9	0	0	0	3	6	9
62	2	5	7	0	0	0	2	5	7
63	1	6	7	0	0	0	1	6	7
64	1	5	6	0	0	0	1	5	6
65	2	7	9	0	0	0	2	7	9
66	2	1	3	0	0	0	2	1	3
67	2	1	3	0	0	0	2	1	3
68	0	1	1	0	0	0	0	1	1
69	0	3	3	0	0	0	0	3	3
70	0	4	4	0	0	0	0	4	4
71	0	4	4	0	0	0	0	4	4
72	0	3	3	0	0	0	0	3	3
73	0	3	3	0	0	0	0	3	3
74	0	2	2	0	0	0	0	2	2
75	0	3	3	0	0	0	0	3	3
76	0	3	3	0	0	0	0	3	3
77	0	1	1	0	0	0	0	1	1
78	1	1	2	0	0	0	1	1	2
79	0	2	2	0	0	0	0	2	2
80	0	1	1	0	0	0	0	1	1
81	0	1	1	0	0	0	0	1	1
82	0	1	1	0	0	0	0	1	1
Total age known	692	281	973	66	9	75	758	290	1,048
Age unknown	3	0	3	2	0	2	5	0	5
Total	695	281	976	68	9	77	763	290	1,053

THE AGE OF PELLAGRINS AT THE TIME OF RECURRENT ATTACKS OF THE DISEASE

In the preceding discussion we have grouped the pellagrins according to their age at the onset of the initial attack. We wish further to consider their behavior in each subsequent year in relation to their age in the year of observation. The point of view is a little different; for example, a pellagrin with onset of the disease in 1911, at the age of 4 years, with recurrence in 1912, 1913 and 1914, has furnished three recurrences to the age group with onset under 5 years in the above discussion. The recurrences appeared, however, when the patient was 5 years, 6 years and 7 years old, respectively. We shall now pay particular attention to the age at the time of recurrence or escape from recurrence.

For the 814 pellagrins who survived the initial attack in a year previous to 1914, there are 1,053 recorded instances of recurrence in a subsequent year, all the events of a single year being counted as one unit recurrence. The distribution of these 1,053 recurrent attacks according to race, sex and age at onset of the recurrent erythema is

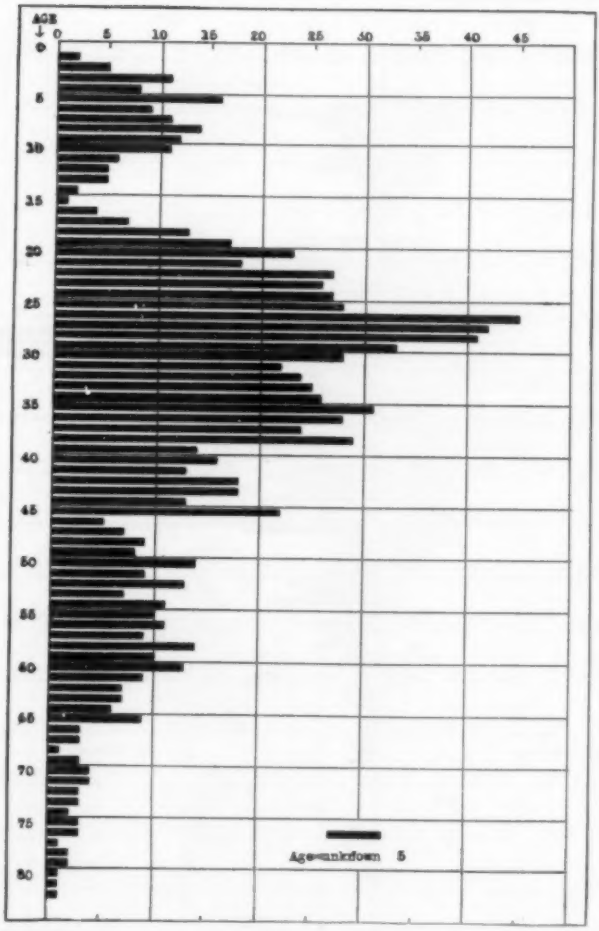

Fig. 6.—Total recorded recurrent attacks of pellagra distributed according to age of the patient at the beginning of the respective recurrent attack.

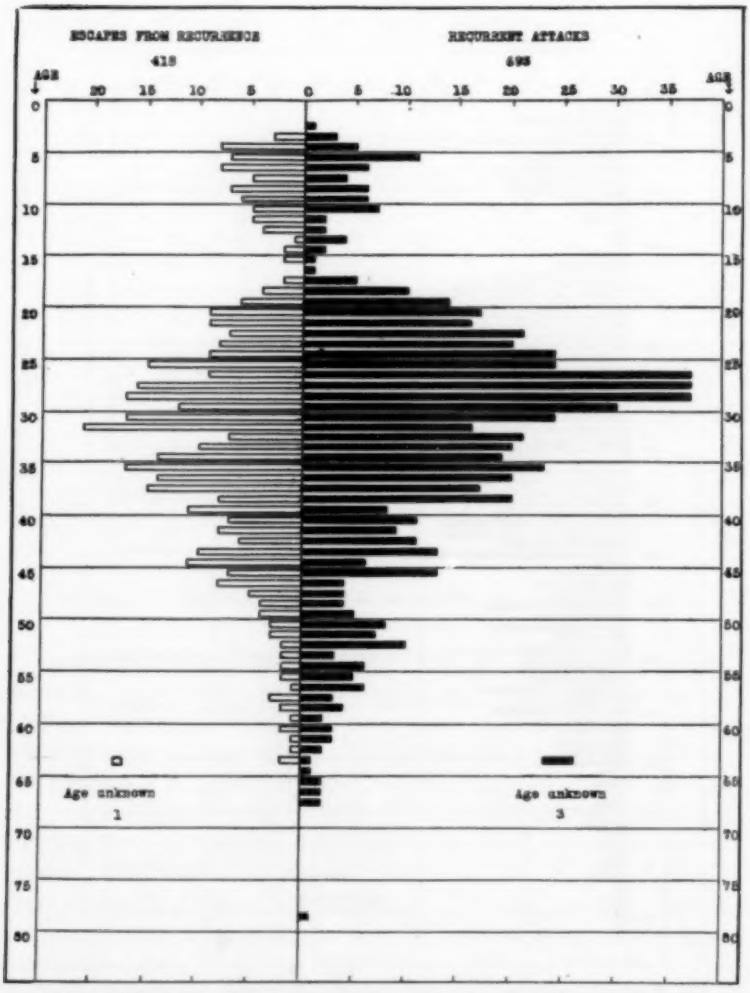

Fig. 7.—Instances of recurrent attack and of escape from recurrence of pellagra in white females, distributed according to age in the year of the respective observation.

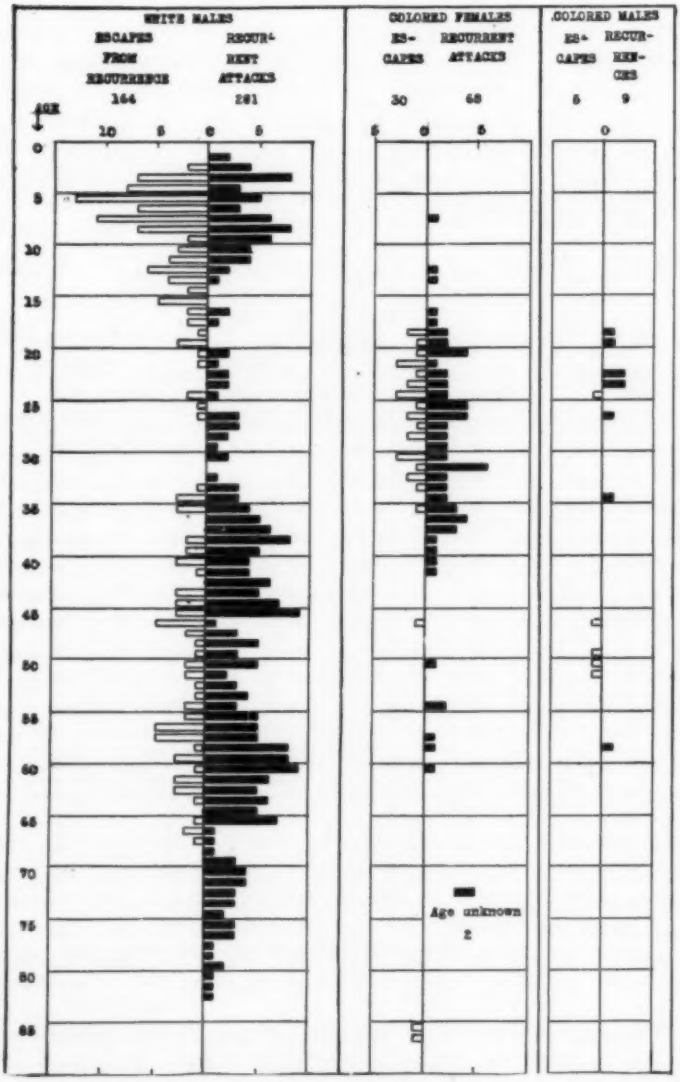

Fig. 8.—Instances of recurrent attack and of escape from recurrence of pellagra in white males, colored females and colored males, distributed according to race, sex and age in the year of the respective observation.

shown in Table 9 and presented graphically in Figures 6, 7 and 8. By comparing these figures with the distribution according to age at the onset of the initial attack shown in Figures 2, 3, 4 and 5 of a preceding paper[2] of this series, one will at once perceive important differences in the age distribution of recurrent and initial attacks of pellagra. The recurrences are relatively less numerous under the age of 10 years and the 15th, 16th and 17th years are especially conspicuous for the small number of recurrent attacks. The recurrences are relatively more numerous in adult life.

TABLE 10.—Distribution of Recurrent Attacks of Pellagra, According to Age at Time of Recurrence, Summarized by Five-Year Age Periods

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0 to 4	9	17	26	0	0	0	9	17	26
5 to 9	33	28	61	1	0	1	34	28	62
10 to 14	17	11	28	1	0	1	18	11	29
15 to 19	31	3	34	6	2	8	37	5	42
20 to 24	98	8	106	11	4	15	109	12	121
25 to 29	165	9	174	14	1	15	179	10	189
30 to 34	100	9	109	15	1	16	115	10	125
35 to 39	88	28	116	10	0	10	98	28	126
40 to 44	50	26	76	2	0	2	52	26	78
45 to 49	30	21	51	0	0	0	30	21	51
50 to 54	34	17	51	3	0	3	37	17	54
55 to 59	20	31	51	2	1	3	22	32	54
60 to 64	10	31	41	1	0	1	11	31	42
65 to 69	6	13	19	0	0	0	6	13	19
70 to 74	0	16	16	0	0	0	0	16	16
75 to 79	1	10	11	0	0	0	1	10	11
80 to 85	0	3	3	0	0	0	0	3	3
Age unknown	3	0	3	2	0	2	5	0	5
Total	695	281	976	68	9	77	763	290	1,053

The data of Table 9 are summarized according to age by 5-year periods in Table 10. The relatively small number of recurrences in pellagrins under the age of twenty years is quite evident. It is of interest to compare the number of observed recurrent attacks with the number of observed initial attacks in persons of the same age in this population. This comparison is shown in summarized form in Table

11. The number of recorded initial attacks was approximately equal to the number of recorded recurrent attacks in the whole group of white females, but under the age of 20 years recurrent attacks were relatively less frequent, constituting only 37 per cent. of the observed attacks in this age group. In women more than 20 years old the recurrent attacks were in the majority. The group of white males showed also a minority of recurrent attacks under 20 years of age, namely 21.1 per cent. of all observed in this age period. In older men, from age 20 to 44 years, the recurrences made up 47.1 per cent. of the observed attacks of pellagra, and after age 45 years they constituted 58.7 per

TABLE 11.—DISTRIBUTION OF INITIAL ATTACKS AND OF RECURRENT ATTACKS OF PELLAGRA OBSERVED IN SPARTANBURG COUNTY, ACCORDING TO RACE, SEX, AND AGE OF THE PATIENT AT ONSET OF THE RESPECTIVE ATTACK

Race and Sex	Age 0 to 19		Age 20 to 44		Age 45 and Over		Total	
	Initial	Recurrent	Initial	Recurrent	Initial	Recurrent	Initial†	Recurrent‡
White females....	152	90	447	501	97	101	710	695
White males.....	121	59	90	80	100	142	315	281
Colored females..	18	8	78	52	20	6	118	66
Colored males....	8	2	12	6	16	1	36	9
Total white.....	275*	140	537	581	197	243	1,026*	976
Total colored.....	26	10	90	58	36	7	154	77
Grand total.....	301*	150	627	639	233	250	1,180*	1,053*

* Including a white child, aged 2, of unknown sex.
† Including pellagrins of unknown age, as follows: thirteen white females, four white males, two colored females.
‡ Including pellagrins of unknown age as follows: three white females, two colored females

cent. of the recorded attacks of pellagra. In the negroes of both sexes the large majority of all attacks of pellagra observed were initial attacks. This relation depends chiefly on the high death rate in negroes in the initial attack for, as we have seen in Table 3, the instances in which negroes survived without recurrence were not very numerous.

THE RELATION OF ESCAPE FROM RECURRENCE TO RACE, SEX AND AGE IN THE YEAR OF OBSERVATION

Whenever a pellagrin survived a whole year without recurrence of the disease, this has been designated as a year without recurrence or as an escape from recurrence. In Table 12 these escapes from recurrence are tabulated according to the age of the patient in the year of

TABLE 12.—Escapes from Recurrent Attack of Pellagra, Distributed According to Race, Sex and Age of the Patient in the Year of Escape

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0
2	0	2	2	0	0	0	0	2	2
3	3	7	10	0	0	0	3	7	10
4	8	8	16	0	0	0	8	8	16
5	7	13	20	0	0	0	7	13	20
6	8	7	15	0	0	0	8	7	15
7	5	11	16	0	0	0	5	11	16
8	7	7	14	0	0	0	7	7	14
9	6	2	8	0	0	0	6	2	8
10	5	3	8	0	0	0	5	3	8
11	5	4	9	0	0	0	5	4	9
12	4	6	10	0	0	0	4	6	10
13	1	4	5	0	0	0	1	4	5
14	2	2	4	0	0	0	2	2	4
15	2	5	7	0	0	0	2	5	7
16	0	2	2	0	0	0	0	2	2
17	2	2	4	0	0	0	2	2	4
18	4	1	5	2	0	2	6	1	7
19	6	3	9	1	0	1	7	3	10
20	9	1	10	1	0	1	10	1	11
21	9	1	10	3	0	3	12	1	13
22	7	0	7	1	0	1	8	0	8
23	8	0	8	2	0	2	10	0	10
24	9	2	11	3	1	4	12	3	15
25	15	1	16	1	0	1	16	1	17
26	9	1	10	2	0	2	11	1	12
27	16	0	16	1	0	1	17	0	17
28	17	0	17	2	0	2	19	0	19
29	12	0	12	0	0	0	12	0	12
30	17	0	17	3	0	3	20	0	20
31	21	0	21	1	0	1	22	0	22
32	7	0	7	2	0	2	9	0	9
33	10	1	11	1	0	1	11	1	12
34	14	3	17	0	0	0	14	3	17
35	17	3	20	1	0	1	18	3	21
36	14	0	14	0	0	0	14	0	14
37	15	0	15	0	0	0	15	0	15
38	8	2	10	0	0	0	8	2	10
39	11	2	13	0	0	0	11	2	13
40	7	3	10	0	0	0	7	3	10
41	8	1	9	0	0	0	8	1	9
42	6	0	6	0	0	0	6	0	6
43	10	3	13	0	0	0	10	3	13
44	11	3	14	0	0	0	11	3	14
45	7	3	10	0	0	0	7	3	10
46	8	5	13	1	1	2	9	6	15
47	5	2	7	0	0	0	5	2	7
48	4	1	5	0	0	0	4	1	5
49	4	1	5	0	1	1	4	5	6
50	3	2	5	0	1	1	3	3	6
51	3	2	5	0	1	1	3	3	6
52	2	1	3	0	0	0	2	1	3
53	2	1	3	0	0	0	2	1	3
54	2	2	4	0	0	0	2	2	4
55	2	2	4	0	0	0	2	2	4
56	1	5	6	0	0	0	1	5	6
57	3	5	8	0	0	0	3	5	8
58	2	1	3	0	0	0	2	1	3
59	1	3	4	0	0	0	1	3	4

TABLE 12.—Escapes from Recurrent Attack of Pellagra, Distributed According to Race, Sex and Age of the Patient in the Year of Escape—(*Continued*)

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
60	2	1	3	0	0	0	2	1	3
61	1	3	4	0	0	0	1	3	4
62	1	3	4	0	0	0	1	3	4
63	2	1	3	0	0	0	2	1	3
64	0	0	0	0	0	0	0	0	0
65	0	1	1	0	0	0	0	1	1
66	0	2	2	0	0	0	0	2	2
67	0	1	1	0	0	0	0	1	1
68	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0
76	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0
86	0	0	0	1	0	1	1	0	1
87	0	0	0	1	0	1	1	0	1
88	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0
Total age known	417	164	581	30	5	35	447	169	616
Age unknown	1	0	1	0	0	0	1	0	1
Total	418	164	582	30	5	35	448	169	617

escape. These are summarized in groups by 5-year age periods in Table 13.

By comparing the data of Tables 12 and 13 with the data of Tables 9 and 10, the significance of race, sex and age in relation to recurrence or nonrecurrence of pellagra in this population may be most clearly seen. This relationship is graphically presented in Figures 7 and 8. White girls under 10 years of age had forty-two recorded recurrences and forty-four recorded escapes from recurrence, the escapes being 51.2 per cent. of the sum. White boys under 10 years of age had forty-five recorded recurrences and fifty-seven recorded escapes from recurrence, the latter amounting to 55.9 per cent. of the sum. In the age period 10 to 14 years the white girls escaped recurrence in just 50 per cent. of the recorded observations, but the white boys escaped in 63.3 per cent. After the age of 15 the sex difference is much more manifest, the girls from 15 to 19 years escaping in 31.1 per cent. of the

observations, while the boys escaped in 81.2 per cent., in this age period. In the age period 20 to 44 years, the white women had 501 recorded recurrences and 287 escapes from recurrence, the escapes amounting to 36.4 per cent. of the sum. In the same age period, the white men had eighty recurrences and twenty-seven escapes, the latter being 25.2 per cent. of the sum. After the age of 45 years there were

TABLE 13.—ESCAPES FROM RECURRENT ATTACK OF PELLAGRA, DISTRIBUTED ACCORDING TO RACE, SEX AND AGE IN THE YEAR OF ESCAPE, SUMMARIZED BY FIVE-YEAR AGE PERIODS

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0 to 4	11	17	28	0	0	0	11	17	28
5 to 9	33	40	73	0	0	0	33	40	73
10 to 14	17	19	36	0	0	0	17	19	36
15 to 19	14	13	27	3	0	3	17	13	30
20 to 24	42	4	46	10	1	11	52	5	57
25 to 29	69	2	71	6	0	6	75	2	77
30 to 34	69	4	73	7	0	7	76	4	80
35 to 39	65	7	72	1	0	1	66	7	73
40 to 44	42	10	52	0	0	0	42	10	52
45 to 49	28	12	40	1	2	3	29	14	43
50 to 54	12	8	20	0	2	2	12	10	22
55 to 59	9	16	25	0	0	0	9	16	25
60 to 64	6	8	14	0	0	0	6	8	14
65 to 69	0	4	4	0	0	0	0	4	4
70 to 74	0	0	0	0	0	0	0	0	0
75 to 79	0	0	0	0	0	0	0	0	0
80 to 84	0	0	0	0	0	0	0	0	0
85 to 89	0	0	0	2	0	2	2	0	2
Age unknown	1	0	1	0	0	0	1	0	1
Total	418	164	582	30	5	35	448	169	617

101 recurrences and fifty-five escapes, or 35.3 per cent. of the sum, in white women, and in white men there were 142 recurrences and forty-eight escapes, the latter amounting to 25.3 per cent. of the sum.

In both sexes there is a very definite indication of increased resistance to recurrence at about the age of puberty. Thus in white girls aged 11 years there were two recurrences and five escapes out of seven observations, and at the age of 12 years there were two recurrences and four escapes out of six observations. This indication of increased resistance quickly disappears, and after the age of 16 the recurrences

predominate. In the white boys, on the other hand, the resistance to recurrence becomes evident at about the age of 12 years, and it disappears very much more gradually, the increased tendency to recur-

TABLE 14.—Relative Frequency of Recurrence of Pellagra in the Definite Records of the 814 Pellagrins Who Survived the Initial Attack of Pellagra Previous to 1914, Grouped According to Race, Sex and Age in the Year of the Respective Observation

Age in Year of Observation	Female			Male			Both Sexes		
	Total Definite Records	Recurrences		Total Definite Records	Recurrences		Total Definite Records	Recurrences	
		Number	Per Cent.		Number	Per Cent.		Number	Per Cent.
White pellagrins									
0 to 4.....	20	9	45	34	17	50	54	26	48.1
5 to 9.....	66	33	50	68	28	41.2	134	61	45.5
10 to 14.....	34	17	50	30	11	36.7	64	28	43.8
15 to 19.....	45	31	68.9	16	3	18.8	61	34	55.7
20 to 29.....	374	263	70.3	23	17	73.9	397	280	70.5
30 to 39.....	322	188	58.4	48	37	77.1	370	225	60.8
40 to 49.....	150	80	53.3	69	47	68.1	219	127	58
50 to 59.....	75	54	72	72	48	66.7	147	102	69.4
60 to 69.....	22	16	72.7	56	44	78.6	78	60	76.9
Over 70.....	1	1	100	29	29	100	30	30	100
Age unknown...	4	3	75	0	0	.....	4	3	75
Total.....	1,113	695	62.4	445	281	63.1	1,558	976	62.6
Colored pellagrins									
0 to 4.....	0	0	.....	0	0	.....	0	0	.....
5 to 9.....	1	1	100	0	0	.....	1	1	100
10 to 14.....	1	1	100	0	0	.....	1	1	100
15 to 19.....	9	6	66.7	2	2	100	11	8	72.7
20 to 29.....	41	25	61	6	5	83.3	47	30	63.8
30 to 39.....	33	25	75.8	1	1	100	34	26	76.5
40 to 49.....	3	2	66.7	2	0	0	5	2	40
50 to 59.....	5	5	100	3	1	33.3	8	6	75
60 to 69.....	1	1	100	0	0	.....	1	1	100
Over 70.....	2	0	0	0	0	.....	2	0	0
Age unknown...	2	2	100	0	0	.....	2	2	100
Total.....	98	68	69.4	14	9	64.3	112	77	68.8
Total, both races	1,211	763	63	459	290	63.2	1,670	1,053	63.1

rence becoming apparent after the age of 25 years. In old age the men show less resistance to recurrence than do the women.

In Table 14 is presented a summary of the data relating to frequency of recurrence, the sum of observed recurrences and recorded

TABLE 15.—Deaths in Recurrent Attack Distributed According to Race, Sex and Age at Onset of the Fatal Recurrence

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0
3	0	1	1	0	0	0	0	1	1
4	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0
7	0	0	0	1	0	1	1	0	1
8	1	0	1	0	0	0	1	0	1
9	0	1	1	0	0	0	0	1	1
10	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0
17	1	0	1	1	0	1	2	0	2
18	1	0	1	0	0	0	1	0	1
19	2	0	2	0	1	1	2	1	3
20	1	0	1	2	0	2	3	0	3
21	0	0	0	0	0	0	0	0	0
22	2	1	3	1	0	1	3	1	4
23	3	0	3	2	1	3	5	1	6
24	1	1	2	0	0	0	1	1	2
25	3	0	3	2	0	2	5	0	5
26	4	0	4	0	0	0	4	0	4
27	3	0	3	0	0	0	3	0	3
28	2	0	2	1	0	1	3	0	3
29	2	0	2	0	0	0	2	0	2
30	2	1	3	0	0	0	2	1	3
31	4	0	4	1	0	1	5	0	5
32	0	0	0	0	0	0	0	0	0
33	2	0	2	0	0	0	2	0	2
34	3	2	5	0	1	1	3	3	6
35	3	0	3	0	0	0	3	0	3
36	4	0	4	0	0	0	4	0	4
37	1	1	2	1	0	1	2	1	3
38	0	1	1	1	0	1	1	1	2
39	0	0	0	0	0	0	0	0	0
40	2	0	2	1	0	1	3	0	3
41	0	1	1	0	0	0	0	1	1
42	0	0	0	0	0	0	0	0	0
43	1	2	3	0	0	0	1	2	3
44	0	2	2	0	0	0	0	2	2
45	5	3	8	0	0	0	5	3	8
46	0	1	1	0	0	0	0	1	1
47	0	0	0	0	0	0	0	0	0
48	0	3	3	0	0	0	0	3	3
49	0	1	1	0	0	0	0	1	1
50	2	1	3	1	0	1	3	1	4
51	0	1	1	0	0	0	0	1	1
52	2	1	3	0	0	0	2	1	3
53	1	1	2	0	0	0	1	1	2
54	2	0	2	1	0	1	3	0	3
55	0	1	1	0	0	0	0	1	1
56	1	1	2	0	0	0	1	1	2
57	0	0	0	0	0	0	0	0	0
58	1	0	1	1	1	2	2	1	3
59	0	2	2	0	0	0	0	2	2

TABLE 15.—Deaths in Recurrent Attack Distributed According to Race, Sex and Age at Onset of the Fatal Recurrence—(*Continued*)

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
60	1	2	3	1	0	1	2	2	4
61	0	1	1	0	0	0	0	1	1
62	0	2	2	0	0	0	0	2	2
63	0	1	1	0	0	0	0	1	1
64	0	1	1	0	0	0	0	1	1
65	1	2	3	0	0	0	1	2	3
66	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0
76	0	2	2	0	0	0	0	2	2
77	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0
79	0	1	1	0	0	0	0	1	1
80	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0
Total age known	64	42	106	18	4	22	82	46	128
Age unknown	1	0	1	1	0	1	2	0	2
Total	65	42	107	19	4	23	84	46	130

TABLE 16.—Deaths in Recurrent Attack, Distributed According to Race, Sex and Age at Onset of the Fatal Recurrence, Summarized by Ten-Year Age Periods

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0 to 9	1	2	3	1	0	1	2	2	4
10 to 19	4	0	4	1	1	2	5	1	6
20 to 29	21	2	23	8	1	9	29	3	32
30 to 39	19	5	24	3	1	4	22	6	28
40 to 49	8	13	21	1	0	1	9	13	22
50 to 59	9	8	17	3	1	4	12	9	21
60 to 69	2	9	11	1	0	1	3	9	12
70 to 79	0	3	3	0	0	0	0	3	3
Age unknown	1	0	1	1	0	1	2	0	2
Total	65	42	107	19	4	23	84	46	130

escapes from recurrence for each age period being taken as the total definite records and the ratio of the observed recurrences to this being expressed as per cent. of the total observations. Thus, in white girls in the age period 0 to 4 years there were nine recurrences and eleven

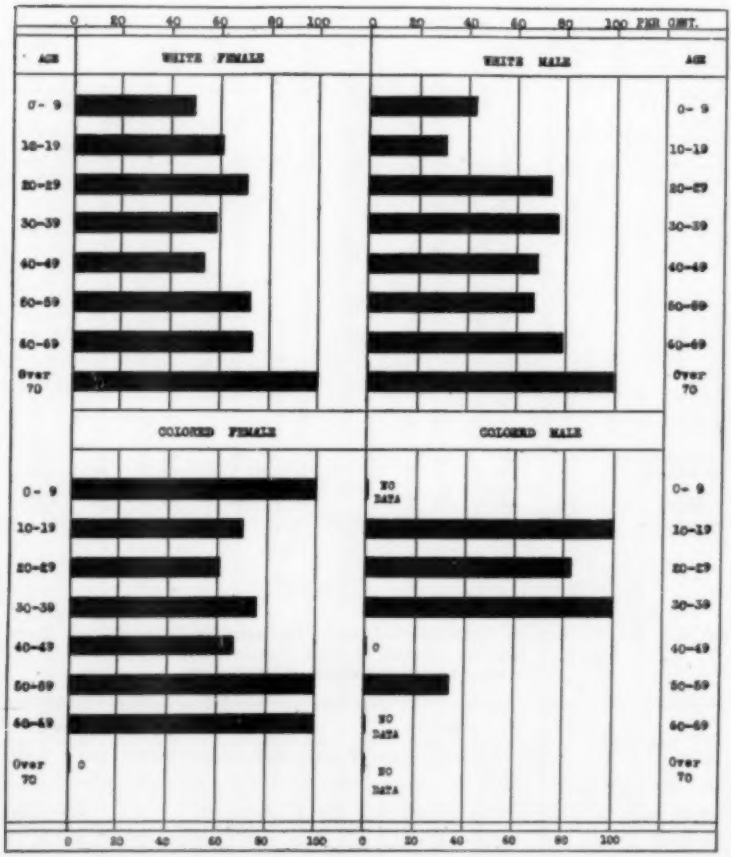

Fig. 9.—Relative frequency of recurrence in each age period for each sex and race, expressed in percentage of the total instances of definite record for the respective age group, according to age at the time of observation.

escapes from recurrence, the recurrences amounting to 45 per cent. of the sum. The relative frequency of recurrence for each decade of life is shown graphically in Figure 9, the length of each bar representing the percentage of recurrences in the total definite records for the respective age group. In the negroes the number of observations for

most of the age periods is very small, so that the percentages have little significance. For the white race, however, they are more significant. The greater frequency of recurrence in older men, the marked tendency for boys from 10 to 19 years of age to escape recurrence and the relatively low recurrence rate in children under 10 years are clearly evident. The women seem definitely more subject to recurrence in the third decade of life than in the fourth or fifth decades and the large number of observations on which these percentages are based in these age periods gives the observed difference considerable significance. Probably this difference may be correlated with the greater frequency of childbirth in the third decade of the life of these women. After the age of 50 the recurrence rate is again relatively high.

THE RELATION BETWEEN DEATH RATE AND AGE AT THE TIME OF RECURRENT ATTACK

The 130 deaths in recurrent attack of pellagra are shown in Table 15, distributed according to race, sex and age at the onset of the fatal attack. In Table 16 the deaths are summarized by 10 year age periods. The great majority of the deaths in recurrence evidently occurred in patients more than 20 years old.

In Table 17 are presented the death rates in recorded recurrent attacks of pellagra for each race and sex by decades of life, the data being taken from Tables 10 and 16. For the white race, as a whole, the death rate in recurrence mounts progressively from 3.4 per cent. in the first decade of life to 18.3 per cent. in the seventh decade. This tendency is also evident in all the race-sex groups, although there are some irregular variations. Thus the white women show their highest death rate, 16.7 per cent., in the sixth decade and the white men show the greatest death rate in the fifth, namely, 27.7 per cent. There were fourteen recurrences in white boys in the second decade of life, without any deaths. The children under 10 years of age are also conspicuous for their low death rate in recurrent attack. The data of Table 17 are presented graphically in Figure 10.

It is probably too early to form a reliable judgment concerning the importance of pellagra in children. The data accumulated during the few years of our study show very clearly a high incidence of pellagra in children residing in the endemic foci of the disease. The vast majority of them survived the initial attack. The tendency for recurrence to appear in the immediately following years is less marked than in adults and the death rate in recurrence, when it does appear, is again very low. At about the age of puberty the tendency to escape recurrence is evidently augmented. The prognosis is therefore comparatively very good in pellagrous children. Whether or not these

children are liable to recurrence after many years is a doubtful question. We think, however, that only a small proportion of them should suffer recurrence in adult life. The question is similar in many ways to the analogous problem in tuberculosis. In the preceding paper[3] of this series it was shown that an escape from recurrence of pellagra

TABLE 17.—Death Rate in Recurrent Attacks of Pellagra for Each Group According to Race, Sex and Age at Onset of the Respective Recurrence

Age at Onset of Recurrence	Female			Male			Both Sexes		
	Recurrent Attacks	Deaths	Rate per Cent.	Recurrent Attacks	Deaths	Rate per Cent.	Recurrent Attacks	Deaths	Rate per Cent.
White pellagrins									
0 to 9	42	1	2.4	45	2	4.4	87	3	3.4
10 to 19	46	4	8.3	14	0	0	62	4	6.5
20 to 29	263	21	8	17	2	11.8	280	23	8.2
30 to 39	188	19	10.1	37	5	13.5	225	24	10.7
40 to 49	80	8	10	47	13	27.7	127	21	16.5
50 to 59	54	9	16.7	48	8	16.7	102	17	16.7
60 to 69	16	2	12.5	44	9	20.5	60	11	18.3
70 to 79	1	0	0	26	3	11.5	27	3	11.1
80 to 89	0	0	.....	3	0	0	3	0	0
Age unknown	3	1	33.3	0	0	.....	3	1	33.3
Total	695	65	9.4	281	42	14.9	976	107	11
Colored pellagrins									
0 to 9	1	1	100	0	0	.....	1	1	100
10 to 19	7	1	14.3	2	1	50	9	2	22.2
20 to 29	25	5	22	5	1	20	30	9	30
30 to 39	25	3	12	1	1	100	26	4	15.4
40 to 49	2	1	50	0	0	.....	2	1	50
50 to 59	5	3	60	1	1	100	6	4	66.7
60 to 69	1	1	100	0	0	.....	1	1	100
70 to 79	0	0	.....	0	0	.....	0	0	.....
80 to 89	0	0	.....	0	0	.....	0	0	.....
Age unknown	2	1	50	0	0	.....	2	1	50
Total	68	19	27.9	9	4	44.4	77	23	29.9

for one year was usually followed by subsequent freedom from the disease, but that even after three or four years, and in one instance after seventeen years without recurrence, an attack of pellagra might again occur. It is therefore not improbable that this large group of children who have recovered from pellagra contains a few individuals who will break down during active adult life and suffer a recurrence of

pellagra. The occasional cases of pellagra appearing in persons who have resided at a distance from the foci of the disease for many years may be instances of this kind.

RELATION OF RECURRENDE TO TREATMENT

The treatment of pellagra presents two phases for discussion, (1) the management of the case during the attack of the disease, and (2)

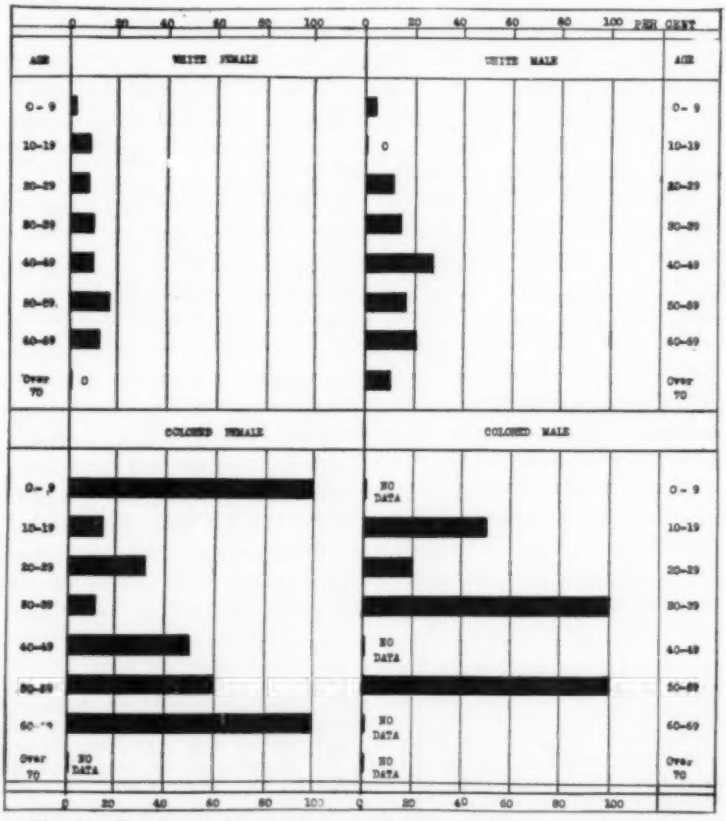

Fig. 10.—Death rate in recurrent attack, expressed in percentage, for each race, sex and 10-year age group, according to age at the time of the recurrent attack.

the management of the patient after recovery from the attack. We hope to present in detail in another paper the records of several cases observed in the hospital during the attack. In the present section we shall consider the record over a period of years of some of the pella-

grins in our series, who have received definite treatment for pellagra at one time or another. The vast majority of the cases in the series have not been given any treatment directed against the disease and this statement is applicable to nearly all of the children. There can be no question, therefore, of the fact that the acute attack of pellagra tends, in the vast majority of patients, to spontaneous recovery. By selecting patients not seriously ill and beginning treatment in the late summer, any conservative physician should be able, with the cooperation of an efficient nurse, to obtain a very large proportion of recoveries. As a rule, those patients who receive treatment receive it during the attack and relatively few continue to be treated during the remainder of the year. Certainly every pellagrin should, if possible, be kept under close medical supervision until at least one summer has passed without any symptoms of the disease.

The first group we wish to consider consists of the fourteen pellagrins who were transported from South Carolina to the New York Post-Graduate Hospital by us in the summer of 1912. These cases were selected for severity in order to provide subjects for observation and study during the acute attack of pellagra and for postmortem examination in the event of death. The details of the treatment and the clinical observations on these patients will not be gone into here. It is sufficient to say that they received a diet of milk and vegetables[4] and no specific drug treatment during the acute attack. In all cases the manifestations of pellagra disappeared and the patients returned to their homes after intervals varying from two weeks to three months. During their stay in the hospital these patients had opportunity to learn by precept and example many things relating to personal hygiene and dietetics. All were white people and all but one of them were women. The summarized record of each of the fourteen patients will be briefly stated.

1. Pellagrin 2131, man, a resident of South Carolina outside of Spartanburg County, was born Nov. 26, 1851, in Union County, S. C. He was a farmer, owning land valued at $2,000. His first attack of pellagra occurred in 1911, the diagnostic erythema appearing in September of that year. He did not regain his strength during the winter. The eruption on the hands recurred in a mild form several times from September, 1911, to June, 1912. He was admitted to the Post-Graduate Hospital on June 4, 1912, and discharged on June 25, 1912, when he returned to his home. During his stay in the hospital the eruption disappeared from his hands and there was a distinct gain in physical and mental vigor, but a net loss in weight from 145 to 144 pounds. His subsequent history is somewhat uncertain. In 1913 there was no definite eruption, but the weakness still persisted. In August, 1913, he weighed 161⅛ pounds. A letter from him in April, 1914, states that he was then still weak and nervous, with subjective burning on his hands, but no eruption as yet.

4. The daily menu of these patients has been published by Myers and Fine, Am. Jour. Med. Sc., 1913, cxlv, 705; First Progress Report, 1914, 111.

2. Pellagrin 1, girl, aged 17 in 1912, had her first attack of pellagra in February, 1911. The erythema recurred in May, 1912. She was brought to New York and admitted to the Post-Graduate Hospital on June 4, 1912. Her symptoms improved almost at once, and she was sent home without recognizable manifestations of pellagra on July 11, 1912. During the latter part of her stay in the hospital she ate maize foods three times a day. Her health remained good during the remainder of 1912, but she suffered recurrence of pellagra in February, 1913, and again in February, 1914.

3. Pellagrin 2, woman, aged 37 in 1912, married and the mother of five children, was a neurotic woman and had been confined in the Columbia state hospital for the insane in the fall and winter of 1912. Her psychosis was of the manic-depressive type. After returning home her initial pellagrous erythema appeared on May 26, 1912. She was brought to New York and admitted to the Post-Graduate Hospital on June 4, 1912. Her admission weight was 94½ pounds. The attack was a severe one and she lay in a typhoid state for several days, her weight diminishing to 85½ pounds. During convalescence the symptoms of mania reappeared and it was deemed advisable to remove her to a special hospital for nervous diseases. After the manifestations of pellagra had disappeared, she was taken home on the earnest demand of her husband on August 15, 1912, but her nervous state was such that he soon had her committed again to the state hospital, where she remained for some months. She gained very rapidly in weight, weighing 114 pounds on Oct. 3, 1912, and her mental disturbance gradually disappeared, so that she was sent home again during the winter. The family sold their farm for about $1,500 and moved to North Carolina, where the patient died early in the spring of 1913 without evident recurrence of pellagra.

4. Pellagrin 9, woman, aged 32 in 1912, suffered her initial attack of pellagra in July, 1910. She escaped recurrence in 1911, but the disease reappeared about June 1, 1912. She was admitted to the Post-Graduate Hospital on July 2, 1912, and discharged free from manifestations of pellagra on July 27, 1912. She returned home and died in April, 1913, without recurrence of pellagra.

5. Pellagrin 12, woman, aged 40 in 1912, suffered her first attack of pellagra in July, 1911, with recurrence in April, 1912. She was admitted to the Post-Graduate Hospital on July 2, 1912, and discharged free from manifestations of pellagra on July 27, 1912. She returned home and remained well during the remainder of 1912. In May, 1913, the disease recurred. During this attack and for some months subsequent to it she received repeated subcutaneous injections of sodium cacodylate. There was a recurrence again in March, 1914, from which she recovered in July, 1914. This patient was a woman of intelligence and refinement and in good financial circumstances.

6. Pellagrin 68, woman, aged 36 in 1912, had her initial attack of pellagra in May, 1911, with recurrence early in July, 1912. She was admitted to the Post-Graduate Hospital on July 16, 1912, and sent home free from recognizable manifestations of pellagra on Aug. 14, 1912. She gained 14 pounds in weight during her stay in the hospital. In 1913 there were repeated mild recurrences of the eruption and she went to Savannah, Ga., where she was treated in the hospital of the U. S. Public Health Service from Feb. 27 to April 1, 1914. In June, 1914, she again suffered a severe recurrence.

7. Pellagrin 113, woman, aged 20 in 1912, suffered her initial attack of pellagra in July, 1912. She was admitted to the Post-Graduate Hospital on July 30, 1912, and discharged free from recognizable manifestations of pellagra on Aug. 27, 1912. The eruption in her case was very extensive, involving lower as well as upper limbs and also extending as a broad belt around the waist. She returned home and remained free from recurrence in 1913 and 1914.

8. Pellagrin 114, woman, aged 18 in 1912, a social intimate of the preceding patient, suffered her initial attack of pellagra also in July, 1912. She was admitted to the Post-Graduate Hospital on July 30, 1912, and discharged free

from recognizable manifestations of pellagra on Aug. 14, 1912. She returned home and remained well during the remainder of the year. In May, 1913, the eruption reappeared and the attack progressed favorably, clearing up early in July. Early in September, 1913, there was another recurrence, which cleared up after about six weeks, but left her weak and emaciated. In January, 1914, the erythema reappeared for about three weeks and left her with well-marked mental derangement. Her family kept her at home, however, and the mental disturbance gradually passed away. About May 1 the erythema reappeared with distressing diarrhea, weakness and emaciation. At this time she was seen by us and, although in distress, she was very clear in her mind and was by no means discouraged in spirit. The symptoms gradually disappeared and in August she appeared well again and was actively at work.

9. Pellagrin 21, woman, aged 28 in 1912, suffered her first attack of pellagra in May, 1911, with recurrence in May, 1912. She was admitted to the Post-Graduate Hospital on Aug. 11, 1912, and discharged free from recognizable manifestations of pellagra on Sept. 6, 1912. Her condition was complicated by a large cystic ovarian tumor, which had been repeatedly tapped and was tapped once during her stay in the hospital. She was advised to have a radical operation late in the fall after her attack of pellagra had subsided, but she was unwilling to undergo the operation. She was sent home, free from recognizable manifestations of pellagra, on Sept 6, 1912. There was a severe recurrence, beginning in April, 1913, and persisting until the middle of July. She died March 4, 1914, without recurrence of pellagra in that year.

10. Pellagrin 115, woman, aged 28 in 1912, suffered her first attack of pellagra in June, 1909, with recurrences in June, 1910, June, 1911, and May, 1912. She was admitted to the Post-Graduate Hospital on Aug. 11, 1912, and sent home free from recognizable manifestations of pellagra on Aug. 27, 1912, having gained 6 pounds in weight. She suffered recurrence in May or June, 1913, and was sent to Savannah, where she was treated in the hospital of the U. S. Public Health Service during the summer. In 1914 she had a severe recurrence beginning early in March and leading to severe mental disturbance and death in the state hospital for the insane in November, 1914.

11. Pellagrin 158, woman, aged 33 in 1912, suffered her first attack of pellagra in July, 1912. She was admitted to the Post-Graduate Hospital on Aug. 17, 1912, discharged on Sept. 26, 1912, and was sent home free from recognizable manifestations of pellagra. There were clear physical signs of active tuberculosis throughout the upper lobe of the right lung and numerous acid-proof bacilli in her sputum. During her stay in the hospital she gained 33 pounds in weight, from 90 pounds on admission to 123 pounds on the day of discharge. After returning home she continued her diet of milk and eggs and has had an outdoor sleeping porch constructed and has slept there regularly. In 1913 she remained well enough to work in the mill, but there was a definite recurrence of the pellagrous erythema in June. She was seen by us on March 26, 1914, at which time there was no evidence of pellagra. The directions in regard to sleeping and diet seemed to be well followed. Unfortunately, it was necessary for her to work all the time. Her weight was then 105 pounds and her voice was somewhat husky. On June 2, 1914, she had a recurrence of the pellagrous erythema accompanied by extreme weakness.

This patient is of some interest because of the recurrence of the pellagrous erythema while she was on a rich diet for the treatment of tuberculosis. Such cases are by no means uncommon in institutions where pellagra and tuberculosis exist together. For example, several cases of pellagra appeared in the cottages and tent colonies of tuberculous patients at the Peoria State Hospital during 1909 and 1910. The existence of such cases seems to have been overlooked by those who would see in the lack of food the essential and sole cause of pellagra.

12. Pellagrin 166, woman, aged 35 in 1912, suffered her first attack of pellagra early in July, 1912. She was admitted to the Post-Graduate Hospital on Aug. 23, 1912, and discharged free from recognizable manifestations of pellagra on Sept. 9, 1912. She returned home and remained free from recurrence of the disease in 1913 and 1914. This patient was an intelligent woman in good financial circumstances and seems to have continued at home the hygienic-dietetic measures which she learned in the hospital.

13. Pellagrin 206, woman, aged 48 in 1912, suffered her initial attack of pellagra in April, 1911, with recurrence in April, 1912. The latter attack was prolonged and an active eruption was still present when she was admitted to the Post-Graduate Hospital on Sept. 5, 1912. She was discharged free from recognizable manifestations of pellagra on Sept. 26, 1912. She suffered a recurrence in September, 1913, and again in April, 1914.

14. Pellagrin 170, woman, aged 34 in 1912, suffered her initial attack of pellagra in June, 1911. She continued at work until late in the summer, when she was confined to bed for several weeks. The attack left her somewhat demented and she was an inmate of the state hospital at Columbia, S. C., from Dec. 12, 1911, to Feb. 7, 1912. About May 15, 1912, there was a recurrence of pellagra. She was selected as an almost hopeless case and sent to New York for observation, being admitted to the Post-Graduate Hospital on Sept. 5, 1912. She then weighed 67 pounds, was extremely weak, rational only at intervals, with eruption involving hands, forearms, arms, shoulders, neck and face. She had an uncontrollable diarrhea and loss of control of bladder sphincter as well. On September 28 she was transferred to the general ward for convalescence, her eruption having disappeared, although the diarrhea and dementia still persisted. Her weight had increased to 75 pounds. On October 3 daily injections of 3 grains of sodium cacodylate were begun and these were daily continued during the remainder of her stay in the hospital. She was sent home on Nov. 18, 1912, weighing 95 pounds and clear in her mind, although somewhat sluggish in her mental activity. She remained free from recurrence in 1913 and 1914, working steadily in the cotton mill. She was seen in May, 1914, and again in September, 1914, and on both occasions her mental activity appeared quite normal.

The ultimate results after two years in this series of fourteen cases lend very little support to the idea that a short period of residence in a hospital can ordinarily be expected to bring about a permanent recovery from pellagra. Only three of these patients remained free from symptoms during the following two years. One of these, Pellagrin 166, was financially able to continue at home the treatment, consisting of rest, strict personal hygiene and nutritious diet, carefully selected and prepared. The other two were mill workers who have been compelled to return to the labor and conditions of their previous lives. It is interesting to note that these two patients, Pellagrin 113 and Pellagrin 170, showed the most extensive cutaneous eruptions observed in any of the cases and that the attack in Pellagrin 170 was the most severe one in the series. We have previously had the opportunity to observe the subsequent freedom from recurrence of patients who survive severe attacks of typhoid pellagra and we are inclined to the opinion that the disease is less likely to recur in such patients.

Two of the pellagrins died early in 1913, before the appearance of a recurrent eruption. One patient, Pellagrin 2131, has probably had

recurrence in both 1913 and 1914, although the evidence is inconclusive. The remaining eight had recurrences in 1913. One of them died early in 1914, without eruption, and seven suffered recurrence again in 1914, one dying of pellagra in November, 1914. These facts are briefly summarized in Table 18.

Among the 1,180 pellagrins in Spartanburg County were several who were treated by injections of sodium cacodylate over a considerable period. In one patient a recurrent erythema appeared on the hands during this course of treatment. We are inclined to the opinion, nevertheless, that the arsenical preparations benefit some patients,

TABLE 18.—SUMMARY OF THE RECORDS OF THE FOURTEEN PELLAGRINS TREATED AT THE POST-GRADUATE HOSPITAL IN 1912

Series No.	Pellagrin Number	Year of Onset	Termination of 1912 Attack	Record in 1913	Record in 1914
1	2131	1911	Recovery	Recurrence ?	Recurrence ?
2	1	1911	Recovery	Recurrence	Recurrence
3	2	1912	Recovery	Died early	
4	9	1910	Recovery	Died early	
5	12	1911	Recovery	Recurrence	Recurrence
6	68	1911	Recovery	Recurrence	Recurrence
7	113	1912	Recovery	Well	Well
8	114	1912	Recovery	Recurrence	Recurrence
9	21	1911	Recovery	Recurrence	Died early
10	115	1909	Recovery	Recurrence	Died of pellagra
11	158	1912	Recovery	Recurrence	Recurrence
12	166	1912	Recovery	Well	Well
13	206	1911	Recovery	Recurrence	Recurrence
14	170	1911	Recovery	Well	Well

especially if given in the interval between acute attacks; not through any specific influence on pellagra itself, but because, in a certain proportion of cases, they promote better nutrition. No doubt other tonic drugs will be found to have a similar value. The use of arsenic during the acute stages of the attack seems to us inadvisable. One advantage of hypodermic medication in pellagra is that it keeps the patient under the constant supervision of his physician and, although this feature is open to abuse as a mere pretext for collecting a fee, it is, nevertheless, of considerable importance to the well-being of the patient in many instances.

There were in this series of cases some pellagrins who were treated with the various secret nostrums, so extensively advertised as pellagra

cures in the South. Some of these patients recovered from their attack and a few have remained free from subsequent recurrences. These are the persons loudest in proclaiming the character of the treatment they had received. In one instance we had the opportunity to observe a severe recurrence in a pellagrin at the same time that his signed testimonial to the "cure" was running in the advertising pages of the local newspapers. The aspects of this business are particularly pernicious in pellagra, because of the ignorance and poverty of the majority of its victims and because the natural evolution of the disease gives in many instances an apparent justification for the claim that it has been cured.

There were in this series of 1,180 pellagrins a considerable number who changed their place of residence to a cooler climate on account of pellagra. It has not been possible for us to follow these patients in a manner sufficiently definite to warrant a detailed discussion of them. We have gained a distinct conviction, however, that pellagrins do much better in a cooler climate. This has been gained in part from the repeated histories of good health enjoyed by pellagrins who moved back to the mountains or who went north to live, and in part from the observation of improvement during a few weeks of cooler weather, in pellagrins under clinical observation, and the rapid failure of pellagrins during a prolonged hot wave. We hope to present an analysis of our data touching on the relation between pellagra and weather conditions in a subsequent communication, and although it is possible this impression may not be substantiated by the actual analysis of the facts, it is stated here as our present judgment.

For the treatment of every pellagrin during the interval between attacks of the disease it is most essential to ascertain and remove the depressing influences. These may be quite various. In institutions the most important handicap is usually dietary, as has long been known. This is also a handicap which is present in a large percentage of the noninstitutional pellagrins in Spartanburg County and we purpose to consider the individual diets of these patients at a later time. The handicap of old age has already been clearly indicated as well as the danger to pellagrous women, of childbirth during the spring and early summer.

In addition to the depressing influences mentioned above, concerning which definite tabulated data have been or will subsequently be presented, we wish to refer to other depressing or predisposing factors which have been observed so frequently in pellagrins that we regard their amelioration or removal, when present, as an important step in the treatment of pellagra. Among these are chronic alcoholism, drug addictions, pulmonary tuberculosis, overwork, chronic dysentery,

pelvic disease in women and hookworm disease in children. The relief of these conditions, when present in pellagrins, seems to us clearly indicated. Unfortunately, our records concerning the association of these conditions with pellagra are not extensive enough to warrant their statistical analysis and we shall therefore rest content with the mere statement of opinion which is based on observation and experience. We are also of the opinion that strict personal hygiene, especially in the care of the mouth and teeth, and the scrupulous avoidance of tainted or contaminated food are important measures in the treatment of pellagra and in the attempt to prevent a recurrence of the disease.

SUMMARY

1. The tendency to recurrence was approximately equal in the two sexes and in the two races considered, the percentage of years with recurrence being 62.4 for white females, 63.1 for white males, 69.4 for negro females and 64.3 for negro males.

2. The death rate in recurrent attacks was 12.3 per cent. for the whole group of pellagrins considered, being considerably below the death rate in initial attack of pellagra for the same group, which was 16.2 per cent.

3. The death rate in recurrent attacks was 9.4 per cent. for white females, 14.9 for white males, 27.9 for negro females and 44.4 for negro males, the variation corresponding roughly to the difference in mortality observed in initial attacks in these groups.

4. White girls who had their initial attack of pellagra before the age of 10 showed a recurrence rate of 46.7 per cent. Those with onset in the second decade of life had a recurrence rate of 67 per cent. and the women with onset at from 20 to 50 years suffered recurrence in 63.5 per cent. of the years for which there are recorded observations. The recurrence rates for the white males with onset in the same age periods were 44, 31.6 and 71.1 per cent., respectively.

5. Recovery from pellagra is much more frequent and more permanent in children than in adults.

6. Recurrence of pellagra after one or more years of freedom from attacks is not uncommon. This phenomenon is especially noticeable in white females of child-bearing age.

7. As compared with initial attacks, recurrences of pellagra are relatively less common in white children because of their tendency to recover and in the colored race because of their high death rate in year of initial attack. Recurrent attacks are relatively more numerous in white men over 44.

8. There is a definite indication of increased resistance to recurrence at about the age of puberty in both sexes of the white race. This resistance is very evanescent in females but continues into the third decade of life in males.

9. The hygienic-dietetic treatment has given good results as far as recovery from the acute attack is concerned. Subsequent recurrence has been observed in a large majority of such cases.

10. Pellagrins who have recovered from very severe attacks seem less liable to recurrence in subsequent years.

11. General measures to increase the resistance of the patient should be continued for at least a year after recovery from the acute attack. Physiologic rest, diet and tonic drugs, as well as strict personal hygiene, should be employed.

12. The successful treatment of complicating disorders is very important in the successful management of pellagra.

EXPERIMENTAL STUDY OF THE MONONUCLEAR CELLS OF THE BLOOD AND TISSUES

WITH SPECIAL REFERENCE TO THE SO-CALLED TRANSITIONAL CELL *

FRANK A. EVANS, M.D.
NEW YORK

The uncertainty that exists in regard to the large mononuclear white blood cells is probably in large part due to the diverse forms they present with the usual stains, and the scarcity of each of these forms in normal blood. The several distinct types represented in this group do not have constant morphologic characteristics demonstrable by the usual stains that admit of a differential classification among them; and only occasionally is a case encountered in which one type stands out predominantly.[1] Similarly the mononuclear wandering cells of the tissues, intimately associated with the mononuclear cells of the blood, are seen in many different forms, and although widely distributed throughout the body, each form is encountered alone in appreciable numbers only in rare pathologic conditions. The relations obtaining among these different mononuclear cells of the blood and tissues is, therefore, in some confusion and the status of each uncertain.

Some of these cells, the so-called transitionals, stand out from all the rest by reason of their content in granules of oxydase ferment, as demonstrable by the indophenol-blue reaction; and some may be recognized wherever encountered by their ability to take vital stains. It has seemed that advantage might be taken of these biologic reactions in clearing up the confusion that exists as to the identity of the different types of mononuclear cells in the blood and tissues. The following study was undertaken with this end in view.

The different forms presented by the mononuclear cells of the blood and tissues has caused a wide variation in nomenclature for cells, many of which are probably identical or closely related to each other, and this tends to deprive us of the advantage of cumulative observation by different authors. But much work has been done, and in view of

* Submitted for publication July 21, 1916.

* From the Pathologic Laboratory, Presbyterian Hospital, New York City.

1. Van Nuys, F.: An Extraordinary Blood, Boston Med. and Surg. Jour., 1907, clvi, 390. Netousek, M.: Endothelium in Stromenden Blute, Folia haematol., 1913-1914, xvii, 407. Bartlett, W. B.: Localized Leukocytosis Associated with Atypical Phagocytic Cells, Pub. Massachusetts Gen. Hosp., 1908-1909, ii, 390. Evans, F. A.: Observations on the Origin and Status of the So-Called Transitional White Blood Cell, THE ARCHIVES INT. MED., 1916, xvii, 1.

that on which these experiments to be reported are based, a brief résumé of the nomenclature, with discussion of the more prominent hypotheses thus far advanced, is essential.

1. Primitive Wandering Cell: This term is applied to an undifferentiated small mononuclear cell of the embryo arising from the original mesenchyme cells recognized by Saxer[2] and Maximow[3] as the mother cell of all the hematogenous and histogenous wandering cells of the body.

2. Resting Wandering Cell: By this name Marchand[4] designates an undifferentiated small round cell considered by him as lymphoid in origin and which, similar to the one mentioned above, is found in the tissues and gives rise to many different cell forms.

3. Clasmatocyte: Ranvier[5] first described under this term a wandering cell of the tissues characterized by a coarse polychrome protoplasmic granulation and frequently long processes that may become separated from the cell. When first described by Ranvier this cell was believed by him to be a derivative of circulating blood elements.

4. Plasma Cell: The small round cells thus named and first described by Unna,[6] which are seen in the tissues in great numbers under some conditions, may be readily recognized by their oval shape and excentrically placed nucleus, with coarse chromatin threads. These are considered as one type of lymphocyte[7] which has either wandered out from the blood stream, or at least is closely related to the lymphoid elements of the blood.

5. Polyblast: Maximow, in his classic studies[8] on the wandering cells of the tissues in inflammatory reactions, identified one type of medium-sized mononuclear constantly present, which he named polyblast. This cell is characterized by great variation in form, which can best be appreciated by reference to the pictures accompanying his articles, but it is predominantly in active tissue reactions a mononuclear round cell having a fairly heavily stained nucleus often irregular in shape, and moderately abundant protoplasm that commonly does not contain any granulation. He asserted that the polyblasts arise in part from emigrated lymphocytes and in part from clasmatocyte-like forms previously in the tissues. He further stated that these cells might become "resting wandering cells" of the tissues, might assume forms resembling the clasmatocytes or those difficult to distinguish from connective tissue elements, all of which have the power to again become round mononuclear wandering cell forms. Under the name of polyblast, Maximow postulates a definite relation between the lymphocytes of the blood and many diverse types of wandering cells, including the clasmatocyte of the tissues.

6. Adventitial Cell: This is a small, round cell, described by Marchand[4] as occurring in the tissues, especially in the region of the blood vessels. He includes in this group the mast cell, the plasma cell, the cell of small round-cell infiltration and others, and maintains that they have the power to produce

2. Saxer, F.: Ueber die Entwickelung und den Bau der normalen Lymphdrusen und die Entstehung der roten und weiszen Blutkorperchen, Anatomische Hefte, 1895-1896, vi, 349.

3. Maximow, A.: Ueber die Entwickelung der Blut- und Bindegewebezellen beim Saugetierembryo, Folia haematol., 1907, iv, 611.

4. Marchand, F.: Ueber Klasmatocyten, Mastzellen, Phagocyten des Netzes, Verhandl. d. deutsch. path. Gesellsch., 1902, iv, 124.

5. Ranvier: Des clasmatocyte, Compt. rend. Acad. d. Sc., 1890, cx, 165.

6. Unna: Ueber Plasmazellen insbesondere biem Lupus, Monatsh. f. prakt. Dermat., 1891, xii, 296.

7. Hertz, R.: Ueber Vorkommen, Natur und Herkunft der Plasmazellen in der Milz, Folia haematol., 1912, xiii, 177.

8. Maximow, A.: Beitr. z. path. Anat. u. z. allg. Path., 1903, xxxiv, 153; Ibid., 1904, xxxv, 93; Ibid., 1905, xxxviii, 301.

highly phagocytic cells and by further change to become leukocytoid and lymphoid cells. They migrate from the tissues into the blood stream and are in turn constantly renewed to the tissues from the blood and blood-forming organs. Marchand questions the close relationship of any of these cells to some forms included by Maximow with the polyblasts, namely, those polyblasts which, remaining in the tissues, assume forms difficult to distinguish morphologically from true fixed tissue elements, and considering the clasmatocyte a fixed tissue derivative does not include it in the class of his adventitial cells. He, in disagreement with Maximow, thus excludes from what he considers the lymphoid mononuclear wandering cells of the tissues any cell that is not readily recognized as a round mononuclear cell; but in addition to the lymphoid reaction in which the adventitial cells are prominent, Marchand recognizes a histogenous reaction,[9] in which cells definitely related to the fixed tissue elements and entirely independent of any of the lymphoid mononuclear cells, are concerned. The cells of this histogenous reaction may also, as those of the the other group, the lymphoid mononuclear wandering cells of the tissues, go over into the blood and appear there as large mononuclear cells. Whereas Maximow included with his polyblast, considered of lymphoid origin, certain wandering cells difficult to distinguish from fixed tissue elements. Marchand sharply divided these into two groups, which may roughly be classified as round cells, lymphoid, and irregular cells, histogenous in origin.

7. Pyrrhol Cell: These cells were first recognized as a distinct entity by their ability to take vital stains and were so named by Goldmann, who used pyrrhol blue among the first of the successful vital stains. They are intimately related to the fixed tissue elements, are of diverse form and ubiquitous in origin, but are specially conspicuous in the milky patches of the omentum, in the liver as the Kupffer cells, and in the reticulum of spleen, lymph glands and bone marrow.[10] These are the cells concerned in the histogenous reaction of Marchand mentioned above, and possibly are the irregular forms included in Maximow's polyblasts.

8. Carmin Cell: Kiyono[11] used lithium carmin as a vital stain, and by this name speaks of essentially the same cells as those described by Goldmann and named pyrrhol cells. He also, with Marchand, maintains that they are active wandering cells of the tissues, concerned in various types of inflammatory reaction, and that they also wander into the blood and are seen there as part of the mononuclear group. In one communication he is inclined to include the transitionals with these histogenous cells.

9. Histiocyte: Thus Aschoff[12] designates those cells which he considers of histogenous origin. He includes in this group the vitally staining cells mentioned above and in agreement with Marchand believes they are seen in the blood as large mononuclears, and that they are not related to the lymphoid cells. Which of the large mononuclear cells of the blood are lymphoid and which are histogenous in origin he does not assert; but his pupil Kiyono later states[13] that although the mother cell of the histiocytes in the tissues and the histiocytes seen in the blood is identical, the cells of this group in the blood are very scarce and a differentiation between them and the other large mononuclear cells is impossible without the vital stain. Kiyono suggests that some

9. Marchand, F.: Ueber die Herkunft der Lymphocyten und ihre Schicksale bei der Entzundung, Verhandl. d. deutsch. path. Gesellsch., 1913, xvi, 5.

10. Goldmann, E. E.: Cellular Activity in Health and Disease; Biochemical Studies Based on New Methods of Intravitam Staining, Lancet, London, 1912, i, 1183.

11. Kiyono, K.: Die vitale Karminspeicherung, Jena, Gustav Fischer, 1914.

12. Aschoff, L., and Kiyono, K.: Zur Frage der groszen Mononuclearen, Folia haematol., 1913, xv, 383.

13. Kiyono, K.: Zur Frage der histiozystaren Blutzellen, Folia haematol., 1914, xviii, 149.

of the large mononuclear and transitional cells of the blood are transition forms of the histiocytes.

10. Macrophage: This term, familiar since Metchnikoff[14] introduced it to indicate any mononuclear phagocytic cell, has been restricted by H. M. Evans[15] to those cells capable of taking the vital stains. While admitting their location and supposed origin in the body as already discussed, Evans calls attention to the fact that these diverse cell forms, sometimes appearing as fixed tissue elements, sometimes as mononuclear wandering cells, have little in common except their ability to take vital stains; and by this only are differentiated from some other wandering cells and fixed tissue elements. He states that these are the cells concerned in tubercle giant cell formation,[16] and, although not venturing any opinion as to their relation to any of the mononuclear wandering cells of the blood, does assert that only very rarely may they be encountered in the peripheral circulation.

11. Endothelial Leukocyte: Mallory[17] in his studies on typhoid fever described the activity of certain cells believed by him to be of endothelial origin, but some of which can now be recognized as those cells capable of taking a vital stain (Pyrrhol cell, Goldmann; Macrophage, Evans). Other cells to which the term endothelial leukocyte was applied by Mallory[18] are those concerned in tubercle formation, osteoclasts of bone, the mononuclear cells of serous surfaces and blood, etc. He maintains that in the tissues they are derived in part from those already in the blood as large mononuclears and in part from the endothelium of the lymphatic system.

More recently, Tschaschin,[19] similarly trying to classify all the mononuclear cells of the body under one head, includes the cells of the milky patches of the omentum (vitally staining cells), those of the serous surfaces and of the spleen and blood forming organs, the small round cells abundant in the region of the blood vessels (Marchand's adventitial cell), in fact all the cells concerned in the lymphoid and histogenous reaction of Marchand, Aschoff, etc., in one group. This composite group, corresponding closely to Mallory's endothelial leukocyte classification, Tschaschin speaks of as histogenous in origin, in that they are all derived from the fixed tissue elements of the primitive mesenchyme. He believes, however, that they are also closely related to the lymphoid system, as evidenced by the appearance in inflammation of the same polyblasts from lymphocytes and these tissue wandering cells.

12. Splenocyte: Pappenheim[20] recognizes as histogenous macrophages (Aschoff's histiocytes) cells which he believes are descendants of the vitally staining cells of the omentum and elsewhere. Some of these which are fixed in the spleen and never go over into the blood he speaks of as splenocytes, and ascribes to them the function of local phagocytosis and elaboration of hemolysin.

---

14. Metchnikoff, E.: Die Lehre von den Phagocyten und deren experimentelle Grundlagen, Handbuch der Pathogenen Microorganismen, Kolle u. Wassermann, Ed. 2, 1913, ii, 655.

15. Evans, H. M.: The Macrophages of Mammals, Am. Jour. Physiol., 1915, xxxvii, 243.

16. Evans, H. M., Bowman, F. B., Winternitz, M. C.: An Experimental Study of the Histogenesis of the Miliary Tubercle in Vitally Stained Animals, Jour. Exper. Med., 1914, xix, 298.

17. Mallory, F. B.: Histological Study of Typhoid Fever, Jour. Exper. Med., 1898, iii, 611.

18. Mallory, F. B.: The Principles of Pathologic Histology, W. B. Saunders Company, Phila., 1914, p. 37.

19. Tschaschin, S.: Ueber die "Ruhenden Wanderzellen" und ihre Beziehungen zu den anderen Zellformen des Bindegewebes und zu den Lymphozyten, Folia haematol., 1913-1914, xvii, 317.

20. Pappenheim, A.: Einige Worte über Histiocyten, Splenozyten und Monozyten, Folia haematol., 1913, xvi, 1.

13. Monocyte: Pappenheim also recognizes a hematogenous macrophage, a circulating blood mononuclear that is also a descendant of the vitally staining cell, but does not arise from those in the spleen. These he speaks of as monocytes, and although he does not admit unreservedly their identity with the wandering cell of Marchand, the macrophage of Metchnikoff, the polyblasts of Maximow, the histiocyte of Aschoff, or the Goldmann pyrrhol cell, he does class together all those mentioned by stating that his monocyte is a descendant of them.

14. Transitional Cell (Uebergangsform): This cell, incorrectly so named by Ehrlich,[21] because, when first recognized by him as a definite entity, it was thought to be a transition form between the large mononuclear and the polymorphonuclear cells of the blood, constitutes an important part of the large mononuclear group of blood cells. It is capable of specific stimulation,[22] but is not even yet generally considered as an independent cell type. When recognized at all it has been ascribed various sources of origin, endothelial (Mallory[18]), histogenous (Aschoff[22]), lymphoid (Pappenheim[23]), and myeloid (Naegeli[24]). It is the only mononuclear cell that contains an oxydase ferment, and to avoid confusion throughout the rest of this paper, it will be designated oxydase mononuclear.

From this brief résumé of part of the literature it is apparent that although all observers quoted admit the close embryologic relation between the connective tissue elements and the wandering cells of the tissues and blood, they are in no way in agreement as to the exact relations existing in the mature organism. Maximow, under the classification of polyblasts, relates the mononuclear cells of the tissues to the lymphoid cells of the blood, and under the same classification describes forms of wandering cells hard to distinguish morphologically from fixed tissue elements. Marchand, through his adventitial cells and derivatives, likewise associates many of the mononuclear cells of the tissues to the blood lymphocytes, but in this group includes, it seems, only mononuclear cells with regular outline, and places the irregular forms, not in the lymphoid group, as Maximow[25] would have it, but in a distinct histogenous system of cells. Marchand believes that these histogenous cells, although entirely distinct from the

21. Ehrlich, P.: Farbenanalytische Untersuchungen zur Histologie und Klinic des Blutes, A. Hirschwald, Berlin, 1891, p. 126.

22. Footnote 1, last reference.

23. Pappenheim, A.: Ueber verschiedene Typen von Lymphozyten und Monozyten, zum Teil im scheinbar normalen Blut, Folia haematol., 1911, xii, 26.

24. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Veit & Co., Leipzig, 1913, p. 180.

25. One cannot be certain, of course, that the irregular cell forms seen by Maximow and classed with polyblasts and therefore to be considered of lymphoid origin, are identical with those of Marchand's histogenous group and therefore vitally staining cells, but from the description and pictures such an assumption seems justified. On the other hand, recalling that Maximow describes transformation of cells readily recognized as emigrated lymphocytes to the irregular forms under discussion, one hardly dares assume that Maximow, even in his careful study, had seen a transformation from a blood lymphocyte to a vitally staining cell, an observation so far not recorded by anyone studying these cells by means of the vital stains.

lymphoid cells, occur in the blood among the large mononuclears. Aschoff, Pappenheim, Kiyono and others similarly see distinct lymphoid and histogenous systems of wandering cells in the tissues and present in the blood in the large mononuclear group; but Pappenheim, while recognizing the cells of this histogenous group by means of the vital stain as the other observers mentioned, thinks those in the blood do not come from the vital staining cells of the spleen (splenocyte); and Kiyono believes that they are not present in great numbers in the blood. In contrast to this division of mononuclear cells into two groups, lymphoid and histogenous, may be mentioned the hypotheses of Mallory and Tschaschin, who include all the different cells in one group, according to Mallory, of endothelial, and to Tschaschin, of histogenous origin. From the literature, then, although it is manifestly unfair to interpret the opinions of the more prominent students of the subject along such narrow lines and without further exposition, one may formulate in general the following different hypotheses: that the different types of mononuclear cells of the blood and tissues are (1) lymphoid (Maximow), (2) endothelial (Mallory), (3) histogenous (Tschaschin), (4) in part histogenous and in part hematogenous (Marchand, Aschoff, Pappenheim, Kiyono).

The oxydase mononuclear (transitional) cell has not been recognized as a distinct entity in many of these studies, and has either been overlooked or included in one or the other group, and thus attributed to every possible source of origin. Pappenheim, speaking of the oxydase mononuclear cells, particularly describes them as myelolymphoidocytes,[23] yet subsequently states that they arise from the vitally staining cells in the milky patches of the omentum, where they may be seen side by side with the vitally staining cells. Kiyono suggests that the large mononuclear transitional cells are transition forms of the histiocytes. Türk[26] denies the relations of these oxydase mononuclear cells to the lymphoid system, and Naegeli[24] considers them specific myeloid elements.

EXPERIMENTAL PART

In view of the uncertainty about the genetic relations of the various mononuclear wandering cells of the tissues and the different large mononuclear cells of the blood, and the difficulty of definitely establishing this relationship by methods so far available, it was deemed advisable, ignoring this phase of the subject entirely, to attempt a classification of the adult cells of the mature organism based on the ability of the different cells to take the vital stain and to give a positive oxydase reaction. Although not definitely proved, it seems likely and is

26. Türk, W.: Vorlesungen über klinische Haematologie, W. Braumiller, Wien und Leipzig, 1904, p. 304.

generally accepted that all the cells capable of vital staining are histogenous (as compared with hematogenous) in origin and will be here so considered without further question; and for lack of a more accurately descriptive term they will be designated throughout what is to follow as *histogenous macrophages.* For the same reason any cell that does not take the vital stain will be considered of hematogenous origin and, if lacking in oxydase ferment, will be considered as ultimately derived from the lymphoid (as opposed to the myeloid) system. By the application of these two biologic reactions under conditions outlined below, whereby cells considered as histogenous (in the common acceptation as described above) may be recognized, and the commonly accepted diagnostic criteria of the lymphoid cells demonstrated, an attempt has been made to determine (1) which of the mononuclear wandering cells of the tissues, if any, are lymphoid and which histogenous; (2) which of the large mononuclear cells of the blood are lymphoid and which, if any, histogenous; (3) if the oxydase mononuclear (transitional) cells of the peripheral blood can be identified on the basis of the reactions employed with any other mononuclear cell of the blood or tissues for which well-recognized diagnostic criteria are available; and (4) whether all the mononuclear wandering cells of the body (exclusive, of course, of the true small lymphocytes) take the vital stain and are therefore after all, as some would have us believe, of histogenous origin.

Technic.—Rabbits were used in all the experiments. The total and differential white blood cell counts in these animals are subject to great variation, as already noted by Moss,[27] but the same cell types as in human blood are present, and there is always a good number of mononuclear cells, a large percentage of which (about 5 per cent. of the total) are typical oxydase mononuclears. Lithium carmin was used as the vital stain because of the contrast accorded with the dark-blue granules of the indophenol-blue reaction. The lithium carmin solution was used in 5 per cent. strength, and made up as advised by Kiyono.[11] The individual dose employed was uniformly 6 c.c. The animals were vitally stained by both intraperitoneal and intravenous injections. While the supply on hand lasted, Grubler's carmin was used, as by Kiyono in his exhaustive studies. In later experiments, because of inability to obtain Grubler's, Merck's carmin was substituted for it. As a vital stain the Merck preparation compared very favorably with that of Grubler, except that the former was more irritating and had a tendency to cause thrombosis of the ear veins after repeated injections and to call out a mild leukocytic reaction in the peritoneal cavity when

27. Moss, W. L., and Brown, G. L.: Variations in the Normal Leukocyte Count in Rabbits, Bull. Johns Hopkins Hosp., 1911, xxii, 258.

injected intraperitoneally. For the demonstration of oxydase ferment the indophenol-blue reaction was used.[28]

Intravenous Vital Staining.—To see which, if any, of the large mononuclear cells of the blood are vitally staining histogenous macrophages, animals were stained acutely and chronically by intravenous administration of the dye, and smears of blood from various vessels, tissue sections, and the omentum were studied microscopically and submitted to the oxydase reaction.

Animals chronically stained by repeated daily doses of filtered lithium carmin showed the usual distribution of carmin-stained cells in the spleen, liver, milky patches of the omentum, and bone marrow as described by Kiyono. But even when the animal was very heavily stained by more than twice the amount of stain used by Kiyono (two courses of seven daily doses separated by six days, and followed in four days by two more doses just before death) no carmin cells were seen in smears of the peripheral blood after careful search of many smears made at different periods during the course of the vital staining. This finding is in accord with results recorded by H. M. Evans,[16] working with trypan blue, Goldmann,[29] using isamin and pyrrhol blue, and Pappenheim[20] and Netousek,[30] who state that rarely do these cells appear in the peripheral capillary circulation. Kiyono and Aschoff,[13] using different substances, including colloidal metal suspensions, although insisting that these cells are normally seen in the peripheral blood,[31] admit that they make up only a very small part of the large mononuclear group. However, with these heavily stained animals, or in those less heavily stained, an occasional carmin cell was seen in the smears made from the portal and splenic vein blood, but even in the most heavily stained animal they were very rare and did not seem to increase appreciably in proportion to the degree of staining. In animals thus stained none of the many carmin cells in the tissues or the

28. Evans, F. A.: The Practical Significance of the Oxydase Reaction as Applied to Blood Cells, Proc. New York Path. Soc., 1915, xv, 143.

29. Goldmann, E. E.: The Process of Digestion Illustrated by the Action of Stains on the Living Tissues, Lancet, London, 1913, ii, 69.

30. Netousk, M.: Ueber Endothelien und ihre Beziehung zu den Monozyten, Folia haematol., 1914-1915, xix, 1.

31. Kiyono did not study smear preparations of the blood, but sections of the various vessels after fixing the animal in toto in formaldehyd. By this method confusing artefactions are likely to occur, for Shipley and Cunningham (Am. Jour. Physiol., 1916, xl, 75) have shown that vital stain may be absorbed through the blood vessels of the omentum and large amounts be suspended free, entirely independent of any cell, in the portal circulation. It is readily conceivable that some of this suspended material might be so placed in relation to the white blood cells in microtome sections of a formaldehyd-hardened vessel full of blood, as to simulate vital staining where in reality none was present. The possible error when intravenous injection of the stain is employed is obvious.

occasional one seen in the blood of the portal system showed a positive oxydase reaction.

A few animals were acutely stained by intravenous injection of 20 c.c. 5 per cent. filtered lithium carmin, a toxic dose that killed the animal in thirty minutes. In these no carmin cells were seen in smears made during the thirty minutes preceding death and after death from the peripheral capillary blood, from arterial blood, or from blood of the splenic and portal veins, although the plasma was a deep pink color. A few minutes after the smear was made many of the nuclei of the leukocytes took on a pink tint as they died, thus proving that the carmin was abundant enough in the plasma, even in the small amounts of it in a smear, to act as a stain.

When unfiltered lithium carmin solution, which was always opaque and showed minute particles under the microscope, was very slowly injected intravenously to avoid death by multiple embolism, often after one and almost always after two doses carmin cells might be seen in the circulating blood. But these cells uniformly gave the oxydase reaction, and with appropriate stains could be identified as polymorphonuclears and as the oxydase mononuclears of the circulating blood.

Intraperitoneal Vital Staining.—To supplement the foregoing and to determine the relations existing between the cells of the omentum and serous cavities to other wandering cells of the body and blood, animals were stained by intraperitoneal injections and studies similar to those described above were made.

Intraperitoneal injection of the filtered lithium carmin solution, even after two courses of twelve daily doses, alone or in combination with intravenous injection, gave the same results as those discussed above for the animals stained by intravenous administration of the filtered stain, except that the milky patches of the omentum were more densely stained. In several animals thus stained the omentum showed many heavily stained carmin cells that did not give the oxydase reaction, side by side with polymorphonuclear and oxydase mononuclear cells which contained no carmin stain; and in two cases the omentum was also infiltrated with many typical plasma cells which showed no carmin staining[32] and did not give the oxydase reaction.

32. As already stated, cells of many different forms take the vital stains and H. M. Evans (Footnote 15) calls attention to the fact that a classification of cells based on their ability to take vital stains crosses all other lines of classification so far employed. In this connection it should be said that in these preparations containing typical plasma cells with no vital staining there were also some mononuclear cells of almost the same size that were vitally stained. This bears out Evans' statement in part and suggests that some such transition as is discussed in Footnote 25 may occur. But the observation made on these preparations can only be considered a remote suggestion of this and admits of no definite conclusion.

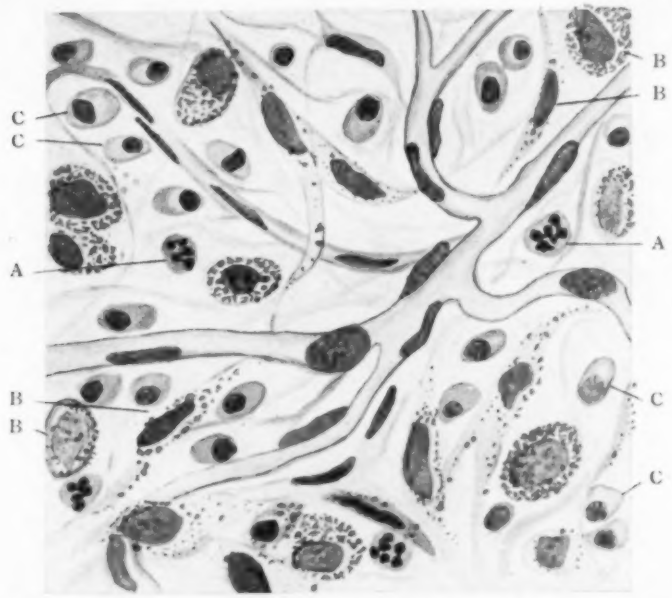

Fig. 1.—Portion of omentum from rabbit vitally stained by intravenous and intraperitoneal injection of filtered lithium carmin solution. The omentum was stretched out on a slide and stained with hematoxylin. It will be noticed that although several different types of both fixed and large wandering cells are heavily stained, the polymorphonuclear and many plasma cells present are entirely free of the stain. *A*, polymorphonuclear cells; *B*, vitally staining histogenous macrophages; *C*, plasma cells.

Fig. 2.—Portion of omentum from rabbit killed one hour after intraperitoneal injection of 10 c.c. unfiltered lithium carmin solution. The omentum was stretched out on a slide and stained with hematoxylin. The stain can be seen in abundance in many of the polymorphonuclear cells present, and in an oxydase mononuclear cell. The histogenous macrophages are unstained. It will be noticed that there is much free stain in the tissues. *A*, polymorphonuclear cells; *B*, histogenous macrophages; *C*, oxydase mononuclear cell.

Never were oxydase mononuclear cells seen except when the polymorphonuclear cells were numerous, and then only after careful search.

It is of further interest that in a vertical section through heavily stained milky patches of the omentum an uninterrupted layer of endothelial cells, reacting differently to carmin and having no oxydase ferment, may be seen running over their peritoneal surfaces, so that these carmin cells are separated from the peritoneal cavity by a continuous sheet of cells of a different type. These peritoneal cells do not contain carmin as compared with the abundant coarse granules of the specifically stained cells, but only a very few fine particles of this stain may be seen in their protoplasm on careful examination with highest magnification. This is in agreement with the observations of Kiyono[11] and of Evans[16] in regard to trypan blue.

When the unfiltered stain was injected intraperitoneally, however, even after one dose and before the vitally staining histogenous macrophages had taken the stain to any extent, the polymorphonuclear and oxydase mononuclear cells in the omentum and peritoneal fluid showed many carmin granules, and under these conditions occasionally an oxydase cell with carmin granules could be found in smears of the splenic vein blood. But even when a mild leukocytic reaction in the peritoneal cavity was called out by a previous injection of weak turpentine solution, no oxydase cells were seen to contain the stain after large doses of filtered lithium carmin.[33]

Mononuclear Cells in Reaction to Localized Bacterial Invasion; Experimental Pneumonia.—To study the different mononuclear cells

33. Similar experiments were undertaken with trypan blue with surprisingly different results, an observation already recorded by Pappenheim (Footnote 20). Trypan blue, a coarse colloidal suspension, differs from lithium carmin in that no particles are seen under the microscope in its unfiltered solution and yet when filtered it is not translucent as is the filtered lithium carmin. Yet no living polymorphonuclear or oxydase mononuclear cell takes up trypan blue when injected intravenously or intraperitoneally, filtered or unfiltered. Evans (Evans, H. M., and Schulemann, W.: The Action of Vital Stains Belonging to the Benzidine Group, Science, 1914, xxxix, 443), bases a hypothesis of the mechanism of vital staining on the size of the colloidal particle, the coarser colloidal suspensions not acting as vital stain only because of their impermeability. Colloidal metal suspensions also act as vital stain (Footnote 12), and Buxton and Torrey (Buxton, B. H., and Torrey, J. C.: Absorption from the Peritoneal Cavity, Jour. Med. Research, 1906, x, 5) have shown that histogenous macrophages will in time take particles as large as red blood corpuscles if made available for them by intraperitoneal injection. Thus we have the histogenous macrophage taking the finest colloidal particle or the red blood cell, and the polymorphonuclear cell refusing any colloidal particle however coarse and not active in the phagocytosis of red blood cells, yet taking microscopic masses of carmin and bacteria. Does this mean that the histogenous macrophage will take any material mass regardless of size, while the polymorphonuclear cell is selective for particles not too large or too small?

in reaction to localized bacterial invasion advantage was taken of the mononuclear character of the early exudate in pneumonia.[34]

In the early exudates in pneumonic processes induced in rabbits by intratracheal injection of various organisms and substances after the method of Meltzer,[35] not only polymorphonuclear but also oxydase and nonoxydase mononuclear cells are to be seen in the exudate in great abundance.[34] The oxydase mononuclears are the same as those seen elsewhere; the nonoxydase mononuclears are made up of a few typical lymphocytes and other larger round cells greatly resembling the polyblast of Maximow. These cells no doubt belong to that great group of mononuclear cells seen in various inflammatory reactions throughout the body. Yet in pneumonia induced in rabbits after they had been heavily stained by combined intravenous and intraperitoneal injections of lithium carmin, neither the oxydase nor nonoxydase mononuclear cells contained the stain, and the few irregularly shaped, vitally stained cells present were either in the alveolar walls or in close association with them.

As further proof that the mononuclear cells in the early exudate in experimentally induced pneumonia in rabbits showing oxydase mononuclear and other cells resembling the polyblasts of Maximow are not vitally staining cells, pneumonia was induced in rabbits poisoned with benzol. Benzol destroys the leukopoietic tissue,[36] but spares the histogenous macrophages, as evidenced by the fact that in vitally stained animals rendered aleukemic by benzol administration, and in which the splenic pulp and bone marrow were largely aplastic, the milky patches of the omentum were as numerous, as cellular, and as heavily stained as in normal vitally stained animals. Yet in pneumonia induced in animals with their leukocytes thus destroyed and with their vitally staining histogenous macrophages unaffected, no cells were seen in the exudate, as already recorded by Winternitz and Hirschfelder.[37]

Mononuclear Cells of Splenic Vein Blood.—To determine, if possible, how active a contributor to the large mononuclear cells of the blood the spleen may be, white cell counts were made of the splenic vein blood at different periods throughout these experiments; and several of these were made simultaneously with counts from the femoral veins, the right and left heart, and the peripheral capillary circulation. Tremendous variations were encountered in both the total

34. Evans, F. A.: The Cytology of the Exudate in the Early Stages in Experimental Pneumonia, Jour. Infect. Dis., 1916, xix, 440.

35. Meltzer, S. J., and Lamar, R. V.: Experimental Pneumonia by Intrabronchial Insufflation, Jour. Exper. Med., 1912, xv, 133.

36. Selling, L.: Benzol als Leukotoxin, Beitr. z. path. Anat. u. z. allg. Path., 1911, li, 576.

37. Winternitz, M. C., and Hirschfelder, A. D.: Studies on Experimental Pneumonia in Rabbits, Jour. Exper. Med., 1913, xvii, 657.

and differential counts, so that the results were not convincing. But in agreement with Morris,[38] these counts all showed a higher mononuclear percentage in the splenic vein than elsewhere, quite independently of the other conditions of the experiment. Of these, a goodly number were typical oxydase mononuclears, some were suggestive of them in appearance but contained no oxydase ferment, and over half were nonoxydase mononuclears. As already stated, carmin cells in the splenic vein blood after staining with filtered lithium carmin were so rare as to be negligible in counting the total of nonoxydase mononuclear cells.

Tissue Culture of Spleen.—In the splenic pulp may be seen many oxydase and many nonoxydase mononuclear cells. In addition, many histogenous macrophages may be recognized by means of the vital stain. For the better differentiation of these cells tissue cultures of spleen[39] from vitally stained animals were grown in a clear medium, and cultures of spleen from a normal animal were grown in a medium containing carmin. In each of these the polymorphonuclear, oxydase mononuclear, and nonoxydase mononuclear cells that wandered out from the planted tissue during the first few days, neither contained carmin nor took it up from the medium. After these cells had died, however, on the second and third day of the original inoculation and in the transplant, many larger mononuclear cells, predominently round, but often angular and spindle shaped, and all heavily stained with carmin, wandered out from the transplanted tissue into the surrounding medium. These cells continued to wander out even in the transplants and after active growth of the connective tissue elements which showed no stain was in progress. In many of these tissue culture preparations giant cells were formed on the cover slip. All of these were heavily stained with carmin and none showed any oxydase ferment.

Foreign Body Giant Cells in Living Animal.—For the more complete study of cells taking part in the formation of foreign body giant cells and to control the observation made in regard to them in tissue cultures, lycopodium spores were injected into the omentum and portal vein of animals that were vitally stained and received several doses of the stain after the introduction of the foreign bodies. In microscopic sections from these animals the carmin cells were relatively scanty, but in close apposition to the foreign bodies, often spread out over their surfaces. And in addition there was frequently an outer layer composed of small, round cells and larger, more irregular mono-

38. Morris, D. H.: The Rôle of the Spleen in Blood Formation, Jour. Exper. Med., 1914, xx, 379.

39. For these tissue culture preparations and help with their interpretation I am indebted to Dr. R. A. Lambert.

nuclears that did not contain the stain. None of these cells showed an oxydase ferment.

In brief, these experiments admit of the following observations:

1. Cells capable of specific vital staining by lithium carmin, the histogenous macrophages, contain no oxydase ferment; and conversely, none of the oxydase-containing cells, the polymorphonuclears and oxydase mononuclears, is specifically stained intra vitam by lithium carmin.

2. The polymorphonuclear and oxydase mononuclear cells phagocyte particles of carmin from the unfiltered solution long before the histogenous macrophages are vitally stained by it.

3. No normal circulating blood cell, either after acute or chronic staining of the animal by the intravenous or intraperitoneal route, takes the carmin stain; and the vitally staining histogenous macrophages are never encountered normally in the peripheral circulation, and only very rarely in the blood of the portal system.

4. In the tissues, in addition to oxydase cells of accidental occurrence, and the vitally staining histogenous macrophages normally present, there may be seen, normally and in reaction to inflammation, foreign bodies, etc., mononuclear wandering cells that contain no oxydase ferment and do not take the vital stain or phagocyte undissolved particles of it. Among these are small round cells resembling tissue lymphocytes and Marchand's adventitial cells, typical plasma cells, and other larger irregular mononuclears resembling pictures of some of Maximow's polyblasts.

5. The blood of the splenic vein contains more large mononuclear cells than blood from other sources. Many of these cells are oxydase mononuclears, but the great majority are nonoxydase mononuclears.

6. In the splenic pulp there are present polymorphonuclear, oxydase mononuclear, nonoxydase mononuclear, and vitally staining cells, each entirely distinct from all the others. The first three types are active, wandering cells and do not survive long in tissue culture preparation. The last does not migrate so actively as the other three under these conditions, survives a relatively long time in tissue culture preparations, and takes part in the formation of foreign body giant cells.

SUMMARY AND CONCLUSIONS

The application of the biologic reactions under the conditions just described, although not affording any information about the remote embryologic relation of the different mononuclear wandering cells or their complete genetic classification, does prove that they are not all of histogenous or lymphoid origin, by the generally accepted criteria, and does justify classification of the adult cells based on biologic

properties. The confusion of names encountered in the literature makes it impossible to place with certainty in this proposed classification many of the cells described, but a few forms of definite morphology, such as the plasma cell of Unna and the *Uebergangsform* of Ehrlich (oxydase mononuclear) can be assigned to one group or another without equivocation.

1. Cells containing an oxydase ferment and not taking the vital stains, the polymorphonuclear and oxydase mononuclear cells (so-called transitionals or *Uebergangsformen* of Ehrlich), primarily of the blood, but seen in the tissues under some conditions.

2. Cells containing no oxydase ferment and specifically stained intra vitam. These cells, recognized by all as intimately associated with the fixed tissue elements and variously termed histiocytes (Aschoff, Pappenheim, Marchand), pyrrhol cells (Goldmann), and macrophages (Evans), are normal constituents of the tissues and of rare and accidental occurrence in the peripheral blood. They present diverse forms in the tissues, some of which can be differentiated from cells included in the next group only by reason of their vital staining.

3. Cells containing no oxydase ferment and not taking the vital stain, the lymphoid elements. To this group belong the true lymphocytes and probably most of the nonoxydase, large mononuclears of the blood (Pappenheim's monocytes); and, in the tissues, the plasma cell of Unna, the polyblasts of Maximow, and the cell of small, round-cell infiltration.

Thus the observations made in these experiments refute the hypotheses of Mallory and Tschaschin that all the adult mononuclears of the blood and most wandering cells of the tissues are of one class, endothelial or histogenous in origin, and support the contention of Aschoff, Pappenheim, and Marchand, that there is a histogenous (capable of vital staining) and lymphoid (incapable of vital staining and containing no oxydase ferment) group distinct from each other. That many vitally staining histogenous cells are included in the large mononuclear group of blood cells, however, as asserted by Aschoff and Pappenheim, seems unlikely from the results obtained in these experiments, in which no vitally stained cells were seen in the peripheral circulation; and the fact that none of these cells anywhere contained an oxydase ferment does not support Kiyono's suggestion that the oxydase mononuclear cells are a type of the vitally staining histogenous macrophages. The higher percentage of mononuclear cells in the splenic vein blood than elsewhere is not in accord with Pappenheim's statement that the large mononuclear cells of the blood (monocytes) are not supplied in any way from the spleen; but our finding that even in the splenic vein the vitally staining histiocytes occur very rarely is in support of his belief that those of the spleen (splenocytes) are not

concerned with the large mononuclear cells of the blood. The observation here recorded that plasma cells, polyblast-like cells, cells of small round-cell infiltration, and some others in reaction to inflammation, and making up part of the cells in the region of foreign bodies, etc., do not stain vitally is not in entire agreement with Marchand, who includes many of these cells in the histogenous group; but rather, although no definite proof has been made available, since they do not contain an oxydase ferment, it appears likely that they are lymphoid cells or even changed forms of emigrated blood lymphocytes. The results obtained by applying the methods of study here employed to tissue cultures of the spleen proves a complete differentiation between the polymorphonuclear and oxydase mononuclear cells in one group, the lymphocytes and nonoxydase mononuclears in another, and the vitally staining histogenous cells in a third, as entirely justifiable in the spleen in accordance with Steudemann's views.[40]

The transitional cell reacts constantly as those of the granulocyte series, in that it contains an oxydase ferment, is not specifically stained intra vitam and takes up carmin particles from the unfiltered solution. It may be seen in the spleen and other blood-forming organs, as admitted by all observers, but is not strikingly more abundant in the splenic vein blood than elsewhere, and is never seen in the omentum, serous fluid or tissues when no polymorphonuclear cells are present. Already sufficient evidence has been adduced that cells of this type are not seen in the uncontaminated lymph of the thoracic duct.[41] These observations, therefore, lead to conclusions contrary to the opinion of Aschoff, Kiyono, Pappenheim, Mallory, Tschaschin and others, that these cells belong to the histogenous group, are lymphoid elements, or of endothelial origin; but in accordance with Naegeli, that they are of the granulocyte series, and together with the neutrophil, eosinophil and basophil, should be considered as descendants of the myeloblasts in the bone marrow and splenic pulp.

In regard to the large mononuclear group of cells as seen in the peripheral blood under normal condition, it may be said that many of them are these transitionals (oxydase mononuclear) of myeloid origin, and none are histogenous, as demonstrated by the power of vital staining. No further statement, however, can be made as to the cells making up this group. No doubt many of them are lymphoid in relation (lymphoblast, Aschoff) and probably some are small lymphocytes that have wandered in the tissues a while, have become changed in form and returned again to the blood. And there is no

40. Steudemann, K.: Phagozytose in der Milz, Folia haematol., 1914, xviii, 140.

41. Davis, B. F., and Carlson, A. J.: Contributions to the Physiology of Lymph, Am. Jour. Physiol., 1909-1910, xxv, 173. Lejeune, E.: Die Zellen im Ductus lymphaticus, Folia haematol., 1914-1915, xix, 371.

reason to believe that endothelial cells may not occur in the vascular system as in other serous cavities,[42] although no morphologic characteristics can be brought forward at present to differentiate them from the lymphoid elements.

In conclusion, therefore, although not venturing any conjecture as to the genetic relation of any one cell type to another, in regard to the adult cells seen in the mature organism it may be definitely stated that (1) the vitally staining histogenous macrophages are not normally encountered in the peripheral blood and occur in the blood of the portal system in such small numbers as to be negligible; that (2) most of the nonoxydase large mononuclear cells of the blood, and those mononuclear wandering cells of the tissues designated as plasma cells, polyblasts, and cells of small round-cell infiltration are not identical with the vitally staining histogenous macrophages, or of myeloid origin, but are probably lymphoid cells or even emigrated blood lymphocytes; and that (3) the so-called transitional cell is not a lymphocyte, any type of histogenous macrophage, or of endothelial origin, but is, with the polymorphonuclear cell, a descendant of the myeloblast and might conveniently be termed the oxydase mononuclear of normal blood.

Johns Hopkins Hospital.

42. It is not intended to convey the impression that all the cells of the serous cavities are endothelial, even under normal conditions. H. M. Evans asserts (Footnote 15) that most of them are vitally staining cells.

PHOSPHATE RETENTION AS A FACTOR IN THE PRODUCTION OF ACIDOSIS IN NEPHRITIS*

W. McKIM MARRIOTT, M.D., AND JOHN HOWLAND, M.D.
BALTIMORE

It is now a well-known and generally recognized fact that acidosis may occur in the course of nephritis, particularly in the terminal stages. Among the evidences of acidosis are a diminished carbon dioxid tension of the alveolar air, an increased hydrogen ion concentration of the blood or serum, a diminution of the alkali reserve and of the oxygen combining power of the hemoglobin.

It is not yet clear on what this acidosis depends. It is surely not due to an accumulation of the acetone bodies, for they do not appear in the urine nor are they increased in the blood. It has been suggested that lactic acid may be responsible for the acidosis. The studies of Lewis, Ryffell and others[1] have shown that lactic acid is not increased in the blood in sufficient amount to account for the acidosis. There is no direct evidence nor, so far as we are aware, is there any indirect evidence that other organic acids can be held responsible. There is a diminished ammonia excretion in many cases of severe nephritis, as Henderson and Palmer[2] have shown. A diminished ammonia production might well be a factor in producing acidosis. A reasonable explanation for the acidosis and one that has been suggested by a number of different writers is that the kidney fails to play its part in excreting the acid substances ordinarily formed.

The regulation of the acid base equilibrium of the body is largely brought about by the ability of the kidney to excrete acid phosphate. This regulation of reaction is one of the most important of the kidney's functions. If this function is interfered with, the normal acid base equilibrium must be disturbed and eventually acidosis is inevitable. In order to prove the failure of this function of the kidney it is neces-

---

*Submitted for publication July 25, 1916.

*From the Harriet Lane Home and the Department of Pediatrics of the Johns Hopkins University.

*We have been led to the investigation of patients outside our immediate field on account of the difficulty of obtaining a sufficient number of cases of severe nephritis in children. We are much indebted to the members of the staff of the Johns Hopkins and Bay View Hospitals for furnishing us with the blood and urine of adult patients and for the use of the histories.

1. Lewis, Ryffell and others: Heart, 1913, v, 45.

2. Henderson and Palmer: Jour. Biol. Chem., 1915, xxi, 37; THE ARCHIVES INT. MED., 1915, xvi, 109.

sary to demonstrate an accumulation of inorganic phosphates in the blood serum.

Greenwald[3] has determined an increase of total phosphorus in the blood serum in some cases of nephritis and with this there was often an increase in his so-called acid soluble fraction, which he believed represented chiefly inorganic phosphates. He suggested no connection between his results and the possibility of acidosis.

It has been necessary to devise a method sufficiently accurate and delicate enough to determine the inorganic phosphates in a small quantity of serum. This we have done.[4] With this method we have determined the inorganic phosphates in the serum of a series of normal adults and older children and then of patients with nephritis, both without and with acidosis.

TABLE 1.—NEPHRITIS WITHOUT ACIDOSIS *

Case No.	Mg. per 100 C.c. P	Mg. per 100 C.c. Cn	Remarks
1	5	8.3	Chronic diffuse nephritis; phenolsulphonephthalein 41 per cent in two hours; nonprotein nitrogen of blood 35 mg.; RpH of serum 8.5; Ambard 0.146.
2	5	10	Chronic diffuse nephritis; fatal; no hyperpnea; RpH 8.5; plasma CO_2 61.4; Ambard 0.137; urea nitrogen in blood 19 mg.
3	4	8	Chronic diffuse nephritis; fatal; phenolsulphonephthalein trace in two hours; RpH 8.5; urea nitrogen in the blood 98 mg.; Ambard 0.775; plasma CO_2 86.
4	2.7	...	Chronic diffuse nephritis; hypertension; condition good; phenolsulphonephthalein 32 per cent. in two hours; RpH 8.5

* The plasma carbon dioxid was determined by the Van Slyke method (Proc. Soc. Exper. Biol. and Med., 1915, xii, 165). The RpH of the serum (alkali reserve) was determined by the Marriott method (The Archives Int. Med., 1915, xvi, 390). Phenolsulphonephthalein determinations were made on two-hour specimens. The nonprotein nitrogen and urea are expressed in terms of mg. of nitrogen per 100 gm. of blood. Chlorids are expressed in terms of sodium chlorid in grams per 100 gm. of blood. Ambard s constant is the urea constant.

The inorganic phosphate, expressed in terms of phosphorus, was low in thirty-five normal persons. The amount varied from 1 to 3.5 mg. per 100 c.c. of blood. In the great majority the amount was less than 2 mg. With marked nephritis there was a tendency for the inorganic phosphate to be slightly increased, but death from nephritis occurred in a number of patients without an increase of the phosphorus and without any evidence of acidosis.

We have determined (Table 2) the inorganic phosphate in the serum of patients with acidosis occurring in nephritis. In every instance there was an increase in the phosphorus to many times the normal amount, that is, to from 8 to 23 mg. per 100 c.c. of blood.

3. Greenwald: Jour. Biol. Chem., 1915, xxi, 29.
4. Howland, Haessler and Marriott: Jour. Biol. Chem., 1916, xxiv; Proc. xviii.

Simultaneous determinations (Table 2) of the combined carbon dioxid of the serum showed that in certain instances the phosphoric acid was combined with twice as much of the available base as was carbonic acid, in striking contrast to the normal conditions in which the base combined with phosphoric acid is only from one tenth to one fifteenth of that combined with carbonic acid.

TABLE 2.—NEPHRITIS WITH ACIDOSIS *

Case No.	Mg. per 100 C.c. P	Mg. per 100 C.c. Ca	Remarks
1	22	4	Chronic diffuse nephritis; fatal; uremia; hyperpnea; RpH 7.8; alveolar CO_2 tension 21 mm.; nonprotein nitrogen of blood 189 mg.; Ambard 1.23; phenolsulphonephthalein 0.
2	11.3	9	Congenital polycystic kidney; improved; hyperpnea; RpH 7.8; plasma CO_2 21; alveolar CO_2 tension 25 mm.; phenolsulphonephthalein trace.
3	19	5.3	Double pyonephrosis; uremia; fatal; hyperpnea; phenolsulphonephthalein 0; urea nitrogen in blood 193 mg.; chlorids 0.538; before alkali; RpH 7.35; plasma CO_2 14.7; alveolar CO_2 tension 10.7 mm.
	12	1	After alkali: RpH 7.9; plasma CO_2 36.6.
4	10.3	7.2	Chronic diffuse nephritis; fatal; nonprotein nitrogen of blood 212 mg.; hyperpnea; RpH 7.95; plasma CO_2 40.
5	13	1.5	Chronic nephritis; lead poisoning; uremia; fatal; hyperpnea; phenolsulphonephthalein 0; before alkali; RpH 7.4; plasma CO_2 11.
	23	4	After alkali; PpH 7.9; plasma CO_2 28.
6	9	6.3	Chronic diffuse nephritis; uremia; fatal; phenolsulphonephthalein 0; RpH 7.9; plasma CO_2 34.
7	8	3.3	Arteriosclerotic kidney; pneumonia; phenolsulphonephthalein 3 per cent.; fatal; RpH 7.8; plasma CO_2 19.
8	9	...	Acute and chronic nephritis; fatal; hyperpnea; phenolsulphonephthalein 32 per cent.; RpH 7.9.
9	18	3	Polycystic kidney; uremia; fatal; hyperpnea; urea in blood 332 mg.; alveolar CO_2 6.4 mg.; Ambard 34.8.
10	9	10	Chronic diffuse nephritis; hypertension; hyperpnea; RpH 7.9; plasma CO_2 52; nonprotein nitrogen in blood 136; chlorids 0.475; Ambard 157.

* See note to Table 1.

The retention of acid phosphate (for approximately 90 per cent. of the phosphate in an average urine is acid phosphate) would seem to be sufficient to account for the degree of acidosis observed. We are not prepared to say that it is the sole factor in producing it.

The retention of acid phosphate in nephritis is not part of a general salt retention; it seems due to a certain specificity of retention, for we have found the inorganic phosphate much increased when there was no increase of sodium chlorid. It is also not necessarily proportional to the total nitrogen and urea retention. The phosphate retention is

not a result of acidosis per se, for we have failed to find an accumulation of phosphates in the serum of severe cases of acidosis in diabetes and other forms of acetone body acidosis. That the high phosphate content is due to interference with a specific function of the kidney and not to increased phosphate production in the body or increased absorption from the intestinal tract is shown by the fact that the urinary output of phosphate is not increased and indeed may be diminished. It is possible to determine a constant for phosphate excretion analogous to Ambard's constant for urea. If, as we believe, the retained phosphate is capable of doing much harm, the constant for phosphate should be of great clinical significance.

The acidosis itself may be overcome by alkali therapy, but it is a matter of experience that little besides this is accomplished. The disease usually progresses to a fatal termination. We have found that the administration of alkali generally fails to bring about a marked reduction of the accumulated phosphate; we have even observed an increase after the administration of sodium bicarbonate.

The accumulated phosphates of the serum, even though neutralized, are capable of doing serious harm to the organism. The amount is sufficient to have a definite influence on the osmotic pressure. This suggests a possible connection with the phenomena of edema and hydremia.

We have found, further, in most of the cases studied a marked reduction in the calcium of the serum. In one case this was only 1.5 mg. per 100 c.c. of serum, as compared with the normal of from 10 to 11 mg. What influence this low calcium content may have on the production of such symptoms as convulsions and hemorrhages can only be suggested. The low calcium content is to be referred to the excess of phosphates in the plasma. It has repeatedly been shown that phosphates administered in any form cause an increased elimination of calcium, chiefly by way of the intestines. The converse is also true. The administration of calcium leads to an increased elimination of phosphate, also by the bowel. This fact offers a suggestion for a rational therapeutic procedure.

VENTRICULAR RESPONSE TO AURICULAR PREMATURE BEATS AND TO AURICULAR FLUTTER*

PAUL D. WHITE, M.D., AND HAROLD W. STEVENS, M.D.
BOSTON

The present communication contains observations on ventricular response to auricular premature beats and to auricular flutter with especial reference to the electrocardiogram.

Auricular premature beats may be attended by normal or abnormal ventricular response, normal or aberrant complexes in the electrocardiogram. Of twenty-three patients with auricular premature beats, whose electrocardiograms were taken at the Massachusetts General Hospital, twelve showed entirely normal ventricular complexes following the abnormal auricular deflections; six showed both normal and slightly aberrant ventricular complexes; four showed normal, slightly aberrant and markedly aberrant complexes, and one showed merely slightly aberrant ventricular complexes. In the electrocardiogram of those patients showing both normal and abnormal or aberrant deflections, the earlier the premature beat the more likely it was to be followed by an abnormal ventricular complex (Figs. 1, 2 and 3). In Figure 1 the earliest premature auricular contractions are entirely blocked; those coming later are followed by abnormal ventricular complexes, and those coming latest of all are followed by entirely normal ventricular complexes.

Auricular premature beats may occur in complete heart block without influencing the ventricular rate or rhythm (Fig. 4).

In auricular flutter one ordinarily expects to find a 2 to 1 auriculoventricular block, with the ventricular complexes in the electrocardiogram of normal shape. In the cases collected by Ritchie twenty-nine showed 2 to 1 block and twenty-two failed to show it; most of the latter showed varying degrees of block, which produced an irregular pulse. Of twelve patients with flutter seen at the Massachusetts General Hospital five showed 2 to 1 block when first seen, while six had irregular pulses due to varying degrees of block; so far as was ascertained, only one of these six had had any digitalis and that one very little. The eleventh patient showed a 1 to 1 rhythm at the beginning of a paroxysm of flutter. After a few minutes at a very rapid rate in which the ventricles kept up with the auricles even at the

* Submitted for publication Aug. 15, 1916.
* From the medical service of the Massachusetts General Hospital, Boston.

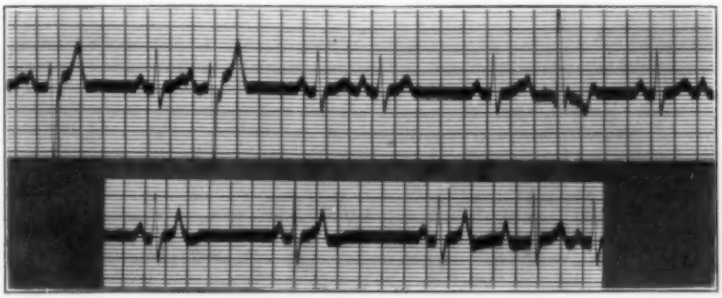

Fig. 1.—Lead II of electrocardiogram of C. S., showing numerous auricular premature beats. In the upper part of the figure the more premature beats show aberrant ventricular complexes, the less premature beat shows a normal ventricular complex. In the lower there are three auricular premature beats without ventricular response; the *P* falls on the *T*. Taken Sept. 1, 1915.

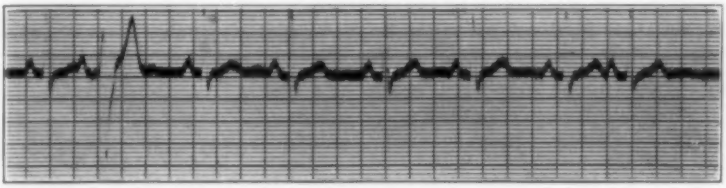

Fig 2.--Lead II of electrocardiogram of C. S., showing two auricular premature beats. The earlier one is followed by an aberrant ventricular complex, the later by a normal ventricular complex. Taken Dec. 3, 1915.

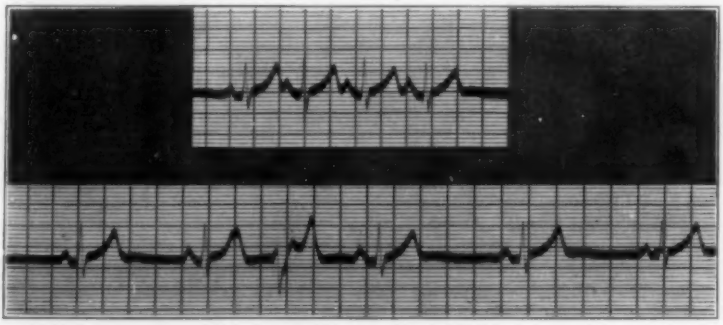

Fig. 3.—Lead II of electrocardiogram of R. M. In the upper part of the figure the premature beats show normal ventricular complexes. In the lower the very premature auricular complex, falling with the *T* deflection, is followed by a markedly delayed aberrant ventricular complex.

speed of 273 per minute, aberrant ventricular complexes suddenly appeared on the electrocardiogram (Fig. 5), suggesting an exhaustion of part of the conduction system (left branch?). Within a few minutes this gave way to a 2 to 1 auriculoventricular block, with the auricles still racing away at high speed. After a quarter hour the rhythm was found to be normal (Fig. 5). The electrocardiogram showing the onset of the change in shape of the ventricular complex is, we believe, unique. The flutter rate was rising from 231 to 273 when the change came, but the increase was gradual and there was no immediate change in rate when the newly shaped ventricular complex appeared. The interventricular intervals over the transition have been measured and found to be in seconds: 0.25, 0.24, 0.26, 0.26, 0.26, 0.23, 0.23, 0.24 | 0.23, 0.24, 0.22, 0.22, 0.22, 0.23, 0.23 . . . 0.23, 0.23, 0.24 . . . 0.24, 0.24, 0.24. The change in shape occurs at the point indicated by the vertical line. The absence of any sudden change in rate and the appearance of 2 to 1 block shortly after favor the view that the change in shape of the ventricular complex is due to aberration, rather than the view that auricular flutter has given way to ventricular flutter. During the taking of this electrocardiogram the change in movement of the string as seen on the screen of the camera suggested at the time the onset of ventricular fibrillation. The ventricular rate recorded in Figure 5 is one of the highest ever recorded graphically. Mackenzie[1] has published a polygram showing a pulse rate of 300 and Lewis[2] an electrocardiogram with a ventricular rate of 270.

The patient who showed the unusual electrocardiogram described above (Fig. 5) was a woman of 38 years, without other obvious abnormality of the heart, except occasional auricular premature beats. She had never suffered any important illness, with the exception of probable phthisis eight years before, of which there were no longer any definite signs. Her complaints were of nervousness, attacks of palpitation and tachycardia first occurring eighteen months before, and circulatory disturbances in the hands just coming on. Roentgen ray showed the presence of right and left cervical ribs, the right being much the larger. An operation was performed and the right cervical rib was removed. This has resulted in decided improvement in the patient's condition. Occasional auricular premature beats still occur, but no further attack of flutter has been recorded, the patient claiming to be free from all except the most transient palpitation. Her hands also have improved, but are not yet normal. The operation was performed in December, 1915.

1. Mackenzie, J.: Diseases of the Heart, London, 1913, p. 246.
2. Lewis, T.: Lectures on the Heart, New York, 1915, p. 116.

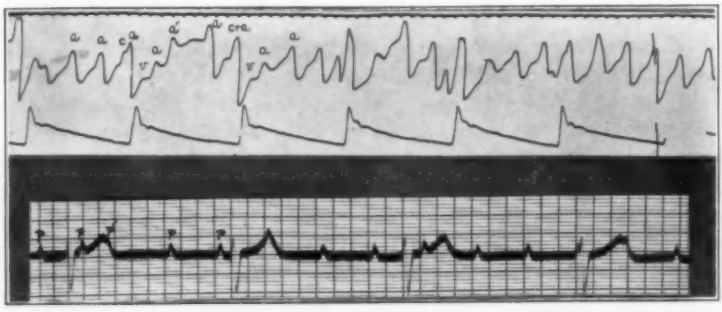

Fig. 4.—Graphic records of J. J. S., the upper part of the figure being a polygram showing complete heart block; *a'* is an auricular premature beat. The lower part of the figure is Lead II of the electrocardiogram, showing complete heart block. *P'* is a premature auricular deflection falling with the *T*.

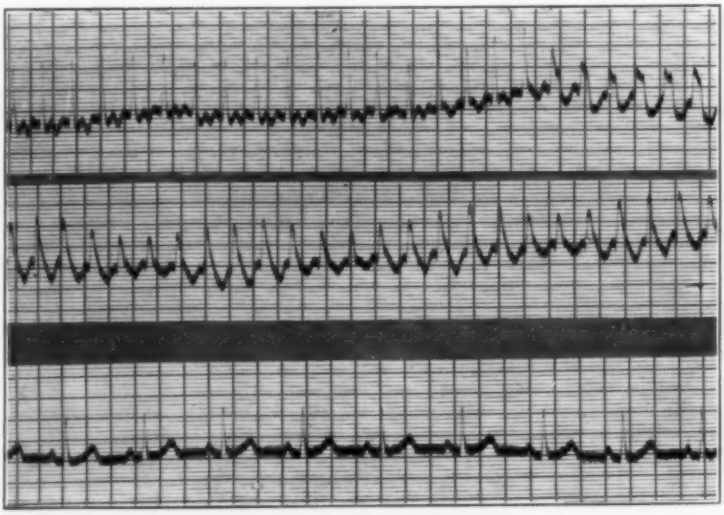

Fig. 5.—Electrocardiograms of F. B. P. The upper part of the figure is Lead II, showing the onset of aberrant ventricular complexes in the course of auricular flutter. The ventricular rate reaches 273 per minute. The middle part of the cut is Lead III, taken immediately after Lead II and showing the aberrant ventricular complexes. The lower part is Lead II taken about fifteen minutes later, showing normal rhythm.

SUMMARY

Twenty-two of twenty-three patients with auricular premature beats studied electrocardiographically showed normal ventricular complexes following abnormal auricular deflections; of these twenty-two, ten showed also aberrant ventricular responses to some of the auricular premature beats; one case showed only aberrant responses. The earlier the auricular premature beat the greater the likelihood of aberration of the ventricular complex responding.

Five of twelve patients with auricular flutter showed 2 to 1 A-V block when first seen, six showed irregular pulses due to variable block, and one showed a 1 to 1 rhythm. In the latter case a remarkable transition, consisting of aberration of the ventricular complexes, occurred between the 1 to 1 and the succeeding 2 to 1 rhythms. A cervical rib seems to have been at least a contributory cause of the flutter in this case.